Evaluating Weekly Circadian Misalignment and the Role it Plays in Type 2 Diabetes Disease Management

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Abstract

Background

Type 2 diabetes (T2D) is a chronic condition and poorer glycemic control in T2D increases the risk of debilitating complications. Sleep and sleep timing have been implicated in both T2D disease risk and management. Chronotype, the behavioural manifestation of phase of entrainment, and social jetlag (SJL), the misalignment between external social time and internal biological time, have been associated with poorer metabolic health. The primary aim of this thesis was to determine how phase of entrainment and living against the circadian clock can influence T2D disease management, with the intention of guiding potential behavioural or educational interventions to improve T2D disease management.

Methods and Results

Chapter 2 was a cross-sectional study which revealed that SJL predicted poorer glycemic control in participants with T2D, while chronotype and personality factors were not significant predictors. A novel interaction between chronotype, SJL and glycemic control was identified; a positive association between later chronotype and HbA1c was only identified in those with the most SJL.

Chapter 3 assessed additional measures of sleep timing variability and metabolic health. This work demonstrated that many measures of circadian misalignment may not measure the same construct. SJL and sleep end variability were moderately associated; however, variability in midsleep, sleep onset and actual sleep duration were not associated with SJL. Furthermore, variability in midsleep, sleep onset and actual sleep duration showed an inverse association with HbA1c in a group of people with well controlled diabetes, suggesting that lower variability was associated with higher HbA1c levels. Why exactly this occurs is unknown, it may be reliant on the characteristics of the sample.

Chapter 4 included two studies which investigated the association between SJL and stress. Study 1 was a cross-sectional study which revealed that SJL was not a significant predictor of general perceived stress or work-related psychosocial stress. Study 2 was an experimental study which demonstrated that SJL did not result in greater reactivity to a physiological stressor. These studies combined suggest that

stress does not mediate the effect of SJL on glycemic control or other indicators of metabolic health.

Chapter 5 described weekly sleep offset differences in a large sample of UK adults. Interestingly, older participants who were not working displayed weekday to weekend day sleep offset differences, albeit to a lesser degree than younger participants.

Chapter 6 qualitatively assessed sleep timing among participants with T2D who were either retired or not currently working. Reducing circadian misalignment may be more feasible among individuals without the daily constraints that come with a regular work schedule. Reflexive thematic analysis of semi-structured interviews revealed that social factors such as quality of TV programs and a desire to maintain a sense of normality when not working led to fluctuating sleeping patterns. Derived zeitgebers from family members also played a role. Those with consistent sleeping patterns had formed healthy habits, had ownership over the environment before bed and good sleep hygiene. They also had some unavoidable curtailments every morning that helped them to form this schedule.

Conclusion

The current findings highlight how common circadian misalignment is and how it may impact T2D management. The findings also provide some rich information on what factors can influence sleep timing beyond work schedules. This paves the way for developing some behavioural and psychoeducational interventions designed to reduce circadian misalignment among those with T2D. This could then reduce the risk of debilitating complications.

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List of Abbreviations

ACTH	Adrenocorticotrophic hormone
AMP	adenosine monophosphate
AMPK1	5’ AMP-activated protein kinase 1
ANOVA	Analysis of variance
ATP	Adenosine triphosphate
BFI	Big five inventory
BMAL1	Brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1
BMI	Body mass index
BP	Blood pressure
BPM	Beats per minute
βTrCP	β-transducing-repeat-containing protein
CBTmin	Core body temperature minimum
CES-D	Centre for epidemiologic studies depression scale
CI	Confidence interval
CK	Casein kinase
CLOCK	Circadian locomotor output cycles kaput
CRH	Corticotrophin-releasing hormone
CRY	Cryptochrome
DBP	D-box binding protein
DCSQ	Demand control support questionnaire
DLMO	Dim light melatonin onset
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
DSPS	Delayed sleep phase syndrome
DYRK1A	dual-specifying tyrosine-(Y)-phosphorylation regulated kinase 1 A
FASPS	Family advanced sleep phase disorder
FBXL3	F-Box and Leucine-rich repeat protein 3
GLUT2	Glucose transporter 2

GLUT5	Glucose transporter 5
GRS	Genetic risk score
GS	Glycogen synthase
GSK3	Glycogen synthase kinase
GSK-3β	Glycogen synthase kinase 3beta
GWAS	Genome wide association study
HbA1c	Glycated haemoglobin
HDL	High density lipoprotein
HLF	Hepatic leukemia factor
HOMA-IR	Homeostatic model assessment for insulin resistance
HPA	Hypothalamic-pituitary-adrenal
HR	Heart rate
ipRGCs	Intrinsically photosensitive retinal ganglion cells
IS	Intradaily stability
IV	Interdaily variability
IQR	Interquartile range
ISCO	International standard classification of occupations
KSS	Karolinska sleepiness scale
L5	Least active 5 hours
LD	Light dark
LDL	Low density lipoprotein
M10	Most active 10 hours
MCTQ	Munich chronotype questionnaire
Med	Median
MEQ	Morningness-eveningness questionnaire
mRNA	Messenger ribonucleic acid
MSF	Midsleep free day
MSFsc	Midsleep on free days sleep corrected
MSW	Midsleep workday
NAD	Nicotinamide adenine dinucleotide

NAD+	Oxidized form of NAD
NADH	Reduced form nicotinamide adenine dinucleotide
NADP	Nicotinamide adenine dinucleotide phosphate
NADPH	Reduced form nicotinamide adenine dinucleotide phosphate
NAMPT	Nicotinamide phosphoribosyl transferase
NCD	Non communicable disease
NFIL3	Nuclear factor, interleukin 3 regulated
OPN4	Melanopsin
OSA	Obstructive sleep apnea
PARP1	Poly(ADP-Ribose) polymerase
p value	Probability value
PER	Period
Pm	Percentage mediation
PSG	Polysomnography
PSS	Perceived stress scale
PSQI	Pittsburgh sleep quality index
PVN	Paraventricular nucleus
RA	Relative amplitude
RHT	Retinohypothalanic tract
RORE	Retinoic acid response element
SBP	Systolic blood pressure
SCN	Suprachiasmatic nucleus
SD	Standard deviation
SDF	Sleep duration free day
SDW	Sleep duration workday
SECPT	Socially evaluative cold pressor task
SGLT1	Sodium-dependent glucose transporter 1
SJL	Social jetlag
SJLabs	Absolute social jetlag
SJLrel	Relative social jetlag

SIRT	Sirtuin
SLOSH	Swedish longitudinal occupational survey of health
SNP	Single nucleotide polymorphism
SNS	Sympathetic nervous system
SO	Sleep onset
SOL	Sleep onset latency
SOf	Sleep onset free day
SOw	Sleep onset workday
τ	Circadian system period
T	Zeitgeber period
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TEF	Thyrotroph embryonic factor
TIB	Total time in bed
TOR	Target of rapamycin
TST	Total sleep time
TTFL	Transcriptional-translational feedback loops
WASO	Wakefulness after sleep onset
ZDF	Zucker diabetic fatty

Publications Arising from this Thesis

Kelly, R. M., Finn, J., Healy, U., Gallen, D., Sreenan, S., McDermott, J. H., & Coogan, A. N. (2020). Greater social jetlag associates with higher HbA1c in adults with type 2 diabetes: a cross sectional study. *Sleep Medicine, 66*, 1-9.

Kelly, R. M., Healy, U., Sreenan, S., McDermott, J. H., & Coogan, A. N. (2022). An Exploratory study of the association of sleep timing variability with cardiometabolic health in healthy middle-aged adults and those with type 2 diabetes. *Chronobiology International, 39*(4), 569-578.

Publications in part arising from this thesis:

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Chapter 1:

Literature Review

1.1 Circadian Rhythms

Most organisms have an endogenous biological rhythm, which persists without environmental time givers, and has been described as *"self-sustained oscillator with an inherent frequency"* (Aschoff, 1965, p. 1427). These are called circadian rhythms, derived from Latin, 'circa' (around) and 'dies' (day), as the endogenous rhythm is usually around 24 hours, but can vary between species (Aschoff, 1965; Baron & Reid, 2014; Roenneberg et al., 2003; Vitaterna et al., 2001). The origin of our knowledge on circadian rhythms can be traced back to Jean Jacques d'Ortous De Marian in the 1700s who identified daily rhythms of leaf opening and closing of the Mimosa plant in the absence of light. De Marian made no inferences about the plant having an internal biological clock and two centuries passed before an endogenous biological clock was identified in humans (Aschoff, 1965). The field of chronobiology came into focus in the second half of the 20th century with Colin Pittendrigh, a pioneer of chronobiology, conducting many experiments that helped determine a great deal of clock biology (Pittendrigh, 1954). There are three key clock properties: firstly, that circadian rhythms are free running rhythms, and the rhythm must be internally generated, and thus remain without any external cues; secondly, that entrainment by external zeitgebers ("time-givers") is possible; and thirdly, rhythms must demonstrate temperature compensation (i.e.) they must maintain themselves over various physiological temperatures (Pittendrigh, 1954; Pittendrigh et al., 1959).

Both endogenous and exogenous cues shape circadian rhythms to promote optimal functioning to meet the changing external world's demands (de Feijter et al., 2020). Nearly all cells in the body display circadian rhythms and they play a crucial role in the organisation of daily life, allowing for optimal fluctuations in physiology and behaviour (Seifalian & Hart, 2019). Physiological functions including metabolism, digestion and energy expenditure in mammals are all organised by the circadian clock system. Further, numerous physiological and behavioural processes in the body such as hormone levels, clock gene expression and body temperature display circadian rhythms (de Feijter et al., 2020; Meule et al., 2012; Tahara & Shibata, 2013). In order to fully understand these circadian rhythms, the master clock, peripheral clocks, the clocks molecular machinery, anatomy, how it synchronises to the external world and its broader influence on physiology and behaviour will be reviewed in the following sections.

1.2 The Hierarchal Circadian Timing System

In circadian physiology, the circadian clock system is composed of a hierarchal network of central and peripheral clocks. A set of neurons and glia cells located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus, just above the optic chiasm, acts as the master clock and sends the time-of-day information to peripheral clocks via both neuronal and hormonal signals (Patke et al., 2020). These peripheral clocks are located in tissues and organs all over the body. For the circadian timing system to function correctly it is pivotal that all clocks are synchronised to each other and to the external environment.

1.2.1 The Master Circadian Clock

The SCN contains the master circadian clock in mammals and this discovery began in the 1970s. Lesioning studies have been seminal to this discovery. Ralph and Menaker (1988) conducted a study which alluded to a mutation with a single, autosomal locus that could alter the circadian period. Following on from this in 1990, Ralph et al. identified the pacemaker role of the SCN by transplanting small neural grafts from the SCN region to tau mutant hamsters. These grafts restored circadian rhythms and the period of the hosts SCN was imposed on the animal receiving the transplant. Interestingly, this suggested that cells of the SCN determine the basic period of the circadian rhythm and adds to the idea that the SCN is the master circadian oscillator (Ralph et al., 1990).

The master circadian clock is composed of ~20,000 neurons and neighbouring glial cells (Gopalakrishnan & Kannan, 2020). This bilateral structure regulates most circadian rhythms in the body and operates as the central player in the circadian timing system (CTS; Moore, 2001). Every neuron in the SCN has a cell-autonomous circadian oscillator that varies from a period of 22-28 hours. However, all these cells undergo a process referred to as coupling via intracellular signaling and as a result, oscillate together to a robust period of around 24 hours (Mohawk et al., 2012). The SCN has two regions: the ventrolateral ‘core’ region and the dorsomedial ‘shell’ region which maintain the circadian rhythm indefinitely with no weakening in its intracellular coupling (Patke et al., 2020). This maintenance is possible as the core and shell regions differ in their efferent projections and ability to maintain intracellular synchrony (Patke et al., 2020). Information on the external environment comes from

the retina to the core SCN; this then projects to the shell SCN. The shell only sends a few projections back to the core. The SCN neurons only engage in very limited neuronal firing at night (Colwell, 2011). They fire steady action potentials throughout the day, commencing at dawn (Colwell, 2011). This clock has a remarkable ability to send information downstream throughout the body to peripheral clocks and this control is coordinated by body temperature, hormones, and the nervous system (Hastings et al., 2018; Patke et al., 2020).

The SCN has a unique ability to generate and sustain oscillations and if the SCN in animals is lesioned, behavioural, physiological, and molecular rhythms are eliminated (Moore & Eichler, 1972; Sakamoto et al., 1998; Stephan & Zucker, 1972). Moore and Eichler (1972) demonstrated how lesioning of the SCN alters physiological functions as light synchronisation of the adrenal corticosterone rhythm was altered. Similarly, its impact on behaviour was demonstrated by Stephen and Zucker (1972). This research highlighted that lesioning of the SCN in rats eliminated circadian rhythms in locomotor activity and drinking behaviour. Finally, Sakamoto et al. (1998) demonstrated that lesioning of the SCN had an impact on a molecular level with a loss of rPER2 mRNA expression in the periphery. This finding has been replicated in subsequent studies (Amir et al., 2004; Jin et al., 1999). The SCN is also very robust and can only be minimally impacted by environmental inputs including temperature. Interestingly, on an individual level, temperature can phase shift SCN cells and peripheral oscillators; however, after intracellular coupling of SCN neurons, temperature signals have no effect (Mohawk et al., 2012).

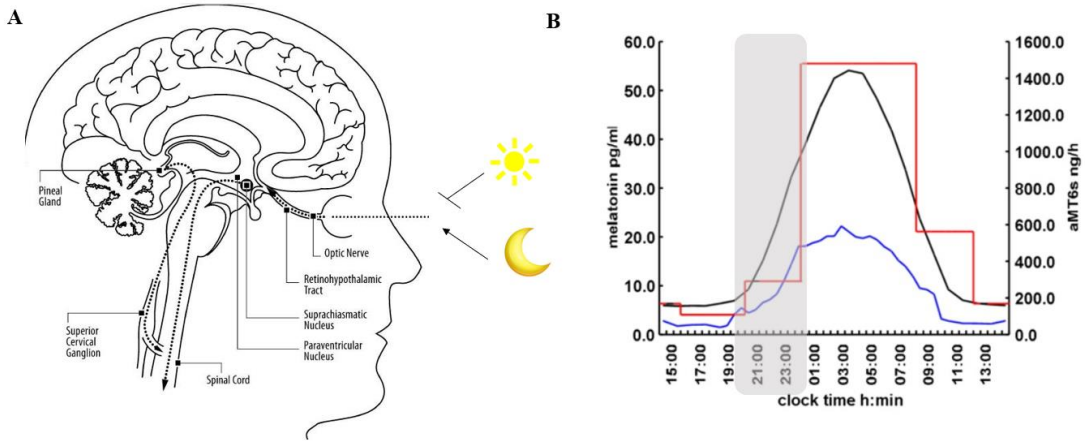
1.2.2 Peripheral Clocks

Endogenous circadian oscillators are in almost every cell in the body, and these are called peripheral clocks (Mohawk et al., 2012). The peripheral clocks receive signals from the master circadian clock and, as such, are not directly entrained by light (Patke et al., 2020). An optimal phase relationship is maintained by these peripheral clocks being responsive to all phase adjustment signals from the SCN (Patke et al., 2020). The organisation of the circadian system requires four processes; endocrine signaling, body temperature, autonomic innervation, and local signals (Mohawk et al., 2012).

The SCN has efferent pathways to other brain regions (mainly hypothalamic) (Schibler et al., 2015). The SCN exerts its neural control over peripheral clocks via both sympathetic and parasympathetic pathways (Kalsbeek et al., 2010; Mohawk et al., 2012). Consider, for example, that daily rhythms in plasma glucose result from sympathetic innervation of the liver signaled by the paraventricular nucleus (PVN) of the hypothalamus (Cailotto et al., 2005; Mohawk et al., 2012). SCN projections have also been shown to relay photic information through autonomic pathways to the adrenal gland (Mohawk et al., 2012). The SCN also sends humoral signals and while many hormones potentially play a role in organising the mammalian circadian clock, melatonin is under strong circadian control. In mammals, the SCN signals the pineal gland to release melatonin in a rhythmic manner, with peak levels occurring at night and minimum levels occurring somewhere around dawn, promoting sleep and wakefulness respectively (Panda, 2016; Figure 1.1). Melatonin release is important for synchronising central and peripheral clocks. Melatonin exerts its effect at two important G-protein coupled receptors: MT1 and MT2. These receptors are widely expressed throughout the body and presumably have functional significance depending on the tissue that they are located in. Their location in the SCN plays a role in entraining circadian rhythms (McArthur et al., 1991). Research has demonstrated that melatonin can be administered to entrain the circadian clock in the absence of light, and it has been shown to reduce jetlag symptoms (Sack, 2010) and circadian misalignment (Marqueze et al., 2021).

Figure 1.1

The rhythmic release of melatonin.



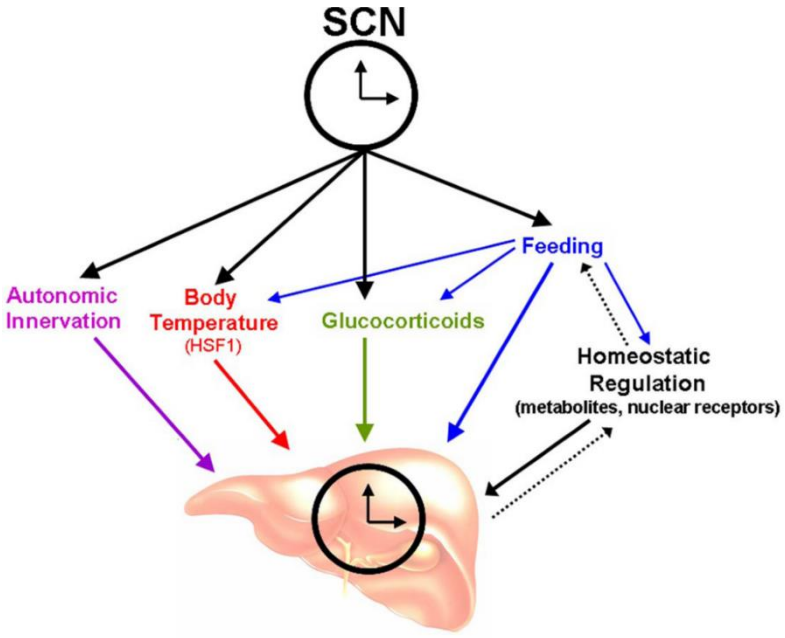
Note. **A** demonstrates the pathway that influences melatonin synthesis and release. Melatonin synthesis is under circadian control through signals from the SCN and light inhibits melatonin. The absence of light is associated with the stimulation of melatonin. During the night neural signals arrive at the SCN, which signals the PVN, the PVN then sends signals to the superior cervical ganglion which signals the pineal gland to release melatonin. Diagram adapted from Doghramji (2007). **B** demonstrates plasma melatonin (black line), saliva melatonin (blue line) and 6-sulphatoxymelatonin (aMT6s) the main urine metabolite of melatonin (red line) in healthy controls. Low melatonin levels are observed during the day and peak levels occur during the night around 3-5 am. DLMO appears to occur somewhere between 8 pm and midnight which can be observed as the increase in the black, blue, and red lines. This is also highlighted with the grey box on the diagram. Diagram adapted from Aulinas (2019). SCN = suprachiasmatic nucleus, PVN = paraventricular nucleus.

Glucocorticoids such as cortisol are a class of steroid hormones that are synthesised by the adrenal glands and released in a regular temporal manner controlled by the SCN (Challet, 2015). Both sympathetic inputs and the underlying rhythm function in both corticotrophin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) yield rhythmic glucocorticoids (Mohawk et al., 2012). Levels increase in the morning and signals are sent to all peripheral clocks with glucocorticoid receptors to synchronise them to the master circadian clock. Further, temporal control of ACTH-induced glucocorticoid release sensitivity is provided by the adrenal clock (Mohawk et al., 2012). Peripheral oscillations can also be modified by circadian rhythms in core body temperature (Patke et al., 2020). The SCN is extremely resistant

to changes in temperature and as a result, circadian temperature cycles are used by the SCN as a global entraining agent for peripheral oscillations (Mohawk et al., 2012). See Figure 1.2.

Figure 1.2

The many ways that the SCN entrains peripheral clocks throughout the body.



Note. Peripheral clocks receive signals from the SCN through autonomic innervation, core body temperature, humoral signals and feeding cues. Some pathways can be activated by local cues without direct input from the SCN. Diagram from Mohawk et al. (2012).

1.3 The Molecular Machinery of the Circadian Clock

The endogenous circadian clock has a distinct ability to maintain ~24-hour rhythms of molecular and cellular activity which can be entrained to the external environment. Signals from the environment (i.e., light/dark cycle) influence the transcription of clock genes in the SCN, and these result in 24-h fluctuations in clock gene proteins. Subsequently, these clock gene proteins influence various clock-controlled genes by binding to their promoter regions and initiating transcription. Circadian clocks on a cellular level have a cell-autonomous oscillator which takes

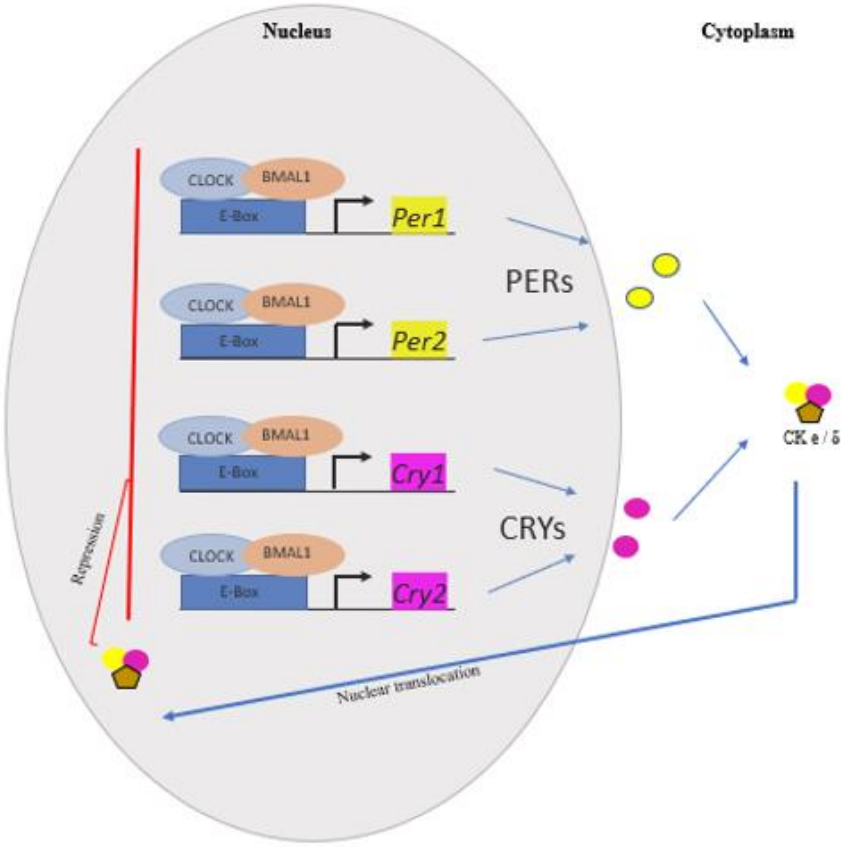
around 24 hours to complete. Cell autonomous clocks are found almost everywhere throughout the body and nearly all cells can generate circadian oscillations (Takahashi, 2017). Interlocking transcriptional-translational based auto-regulatory feedback loops (TTFLs) in the suprachiasmatic nucleus (SCN), CNS sites and peripheral tissues run these molecular circadian clocks in mammals, which underpin system wide circadian timekeeping (Patke et al., 2020; Takahashi et al., 2017). These endogenous timers are thought to be the result of convergent evolution as all transcriptional circuits have a dominant aspect which is negative feedback with delay (Takahashi, 2017).

The primary loop is composed of two positive regulators *BMAL1* (brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1) and *CLOCK* (circadian locomotor output cycles protein kaput) which belong to the basic helix-loop-helix (bHLH)-PER-ARNT-SIM (PAS) family of transcription factors (Patke et al., 2020; Reppert & Weaver, 2001). In this primary loop, the translational products of *CLOCK* and *BMAL1* dimerise to activate the transcription of negative elements which are part of the period (PER) and cryptochrome (CRY) family in a set of rhythmic genes. The transcription of these target genes (*PER1*, *PER2*, & *PER3*; *CRY1* & *CRY2*) becomes activated during the day by heterodimers of CLOCK-BMAL1 interacting with E box elements in their enhancer and/or promoter regions (Patke et al., 2020). These PER and CRY proteins build up in the cytoplasm forming heterodimers before translocating to the nucleus, towards the end of the day. Notably, this translocation is mediated by serine threonine kinases, casein kinase I epsilon (CKIε) and casein kinase I delta (CKIδ). PER and CRY form a complex with CKIε/δ, and phosphorylation leads to alterations in stability and enhanced nuclear entry (Ko & Takahashi, 2006; Lowrey & Takahashi, 2011; McClung, 2007). When these complexes containing PER and CRY build up in the nucleus, they interact with the CLOCK-BMAL1 heterodimer, which in turn inhibits continued production of PER and CRY (see Figure 1.3; Patke et al., 2020). PER and CRY proteins are degraded towards the end of the night and once they drop, transcription mediated by *CLOCK* and *BMAL1* is activated again and the cycle is complete (Albrecht & Eichele, 2003; Patke et al., 2020). The degradation of PER and CRY is crucial here to allow a new cycle to begin and for correct 24-hour timing. CK1ε/δ phosphorylates PER 1 and 2 making them targets for subsequent ubiquitination and degradation by β-transducing-repeat-containing protein (βTrCP) and 26s proteasome (Buhr & Takahashi, 2013). CRY 1 and 2 are not phosphorylated

or targeted for ubiquitination by the same mechanism. 5'AMP-activated protein kinase 1 (AMPK1) phosphorylates CRY1 and a sequential dual-specifying tyrosine-(Y)-phosphorylation regulated kinase 1 A (DYRK1A) / glycogen synthase kinase 3beta (GSK-3β) cascade phosphorylates CRY2 (Buhr & Takahashi, 2013; Camacho et al., 2001; Lamia et al., 2009). Ubiquitination and degradation then occurs via F-Box and Leucine-rich repeat protein 3 (FBXL3; Ribas-Latre & Eckel-Mahan, 2016). Some posttranslational modifiers and additional feedback loops work also to modulate the period of this primary loop (Oster, 2020). A role for these clock genes in humans was established in research that shows that core genes such as *PER2* play a primary role in some human sleep timing disorders, including family advanced sleep phase disorder (FASPS; Takahashi., 2017).

Figure 1.3

The primary feedback look of the molecular circadian clock in mammals.



Note. A simplistic schematic diagram of the primary transcriptional translational feedback loop. The primary loop contains positive elements CLOCK-BMAL1, which bind to E-box elements and activate the transcription of negative elements in the PER and CRY family. PER and CRY protein products heterodimerise and with the help of casein kinase (CK e / δ), translocate from the cytoplasm into the nucleus. When PER and CRY build up, they inhibit CLOCK-BMAL1 activity. PER/CRY then decrease and a new cycle of transcription by CLOCK-BMAL1 is activated. Figure was adapted from Takahashi (2017).

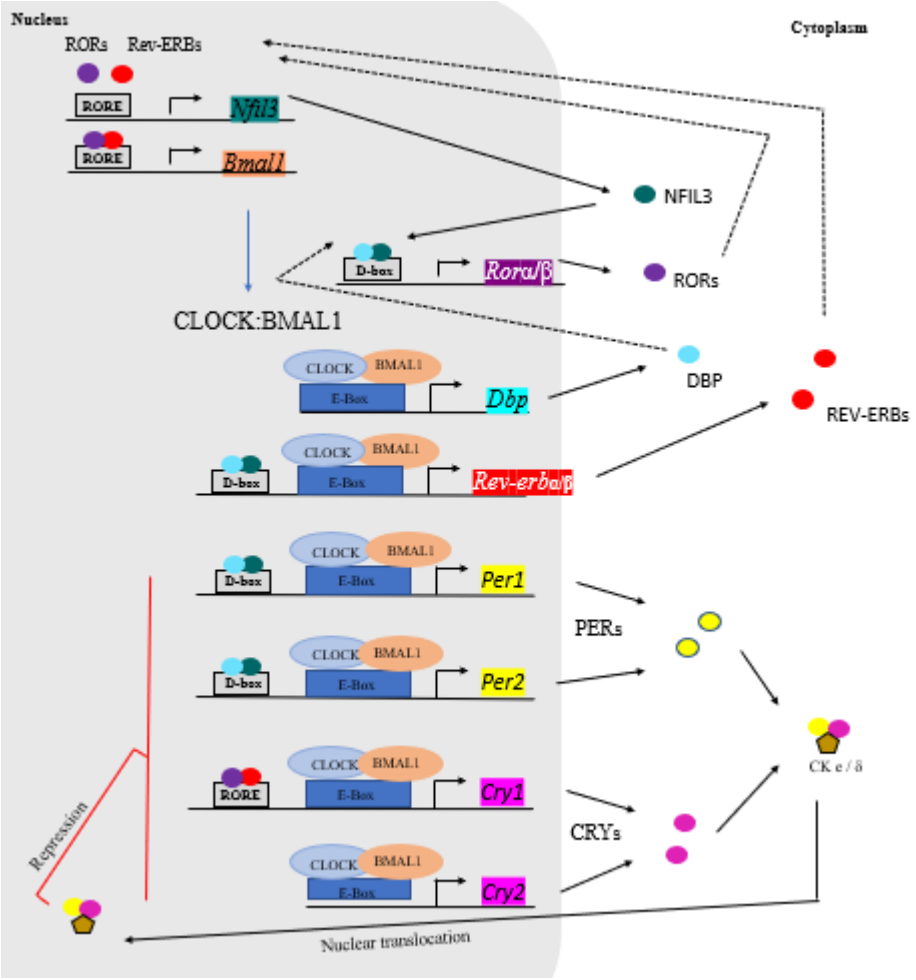
The primary TTFL discussed above is accompanied by a second auxiliary loop involving the retinoid-related orphan receptors RORα and REV- ERBα, which drive the rhythmic expression of *BMAL1* (Green et al., 2008; Solt et al., 2011). This loop operates predominantly to stabilise the primary loop (Nader et al., 2010). Retinoic acid response elements (ROREs) in promoter and enhancer region of target genes including

BMAL1 are competed for by the REV-ERBα and RORα (Sato et al., 2004). Transcription is activated by RORα and repressed by REV-ERBα and the rhythmic changes in ROR/REV-ERB occupying ROREs drives the *BMAL1* rhythmicity (Green et al., 2008). REV-ERBα levels are robustly rhythmic due to CLOCK/BMAL1 activating the transcription of the *REV-ERBα* gene and inhibition by PER/CRY. This causes the alternating occupancy on ROREs. Research has also suggested that in order for RORα to be in phase it requires the gene *clock* (Sato et al., 2004). These are two crucial TTFL loops in the core clock machinery; they are interlocked forming a canonical positive – negative feedback network (Sato et al., 2004).

Additional loops linking cell metabolism and the clock are being identified which indicates that a web of interconnected negative feedback loops exist in the form of a genetic network that regulates the transcription of core clock genes in addition to output genes (Welsh et al., 2010). A third CLOCK-BMAL1 driven transcriptional loop involving a separate set of PAR bZIP factors, D-box binding protein (DBP), thyrotroph embryonic factor (TEF), and hepatic leukemia factor (HLF) exists (Takahashi, 2017). The target of these three proteins are D-boxes and here they interact with the repressor NFIL3 (Nuclear Factor, Interleukin 3 regulated) which is driven by the REV-ERB/ROR loop (Takahashi, 2017; see Figure 1.4). Depending on the cis elements in the target gene (i.e., E-box, RORE, or D-box), they generate cycles of transcription with different phases of expression resulting in rhythmic biological outputs (Takahashi, 2017; see Figure 1.4). Previous work has suggested that somewhere between 10% and 40% of the rodent genome displays ~24-hour rhythms in expression. Furthermore, a recent study on male baboons, a closer relative to humans, identified that more than 80% of protein-coding genes detected from 64 different tissues and brain regions demonstrated 24-hour rhythms in expression, in at least one tissue (Mure et al., 2018).

Figure 1.4

A more advanced diagram of the molecular circadian clock in mammals.

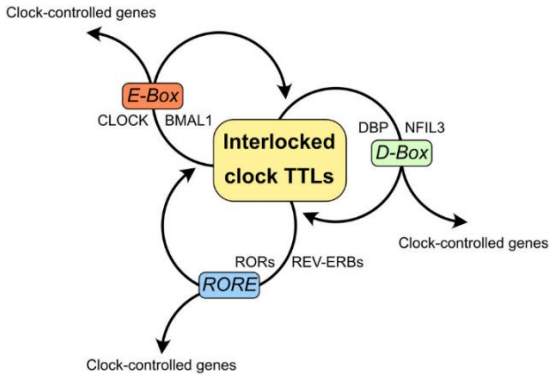


Note. A detailed view of the complexity of the molecular machinery. The primary loop shown in Figure 1.3 can still be observed, however, the two further auxiliary loops are also shown. *CLOCK* and *BMAL1* also regulate the REV-ERBS which rhythmically repress *BMAL1* and *NFIL3* transcription. RORs on the other hand activate *BMAL1* and *NFIL3* transcription. NFIL3 protein products in turn repress DBP in order to regulate ROR nuclear receptors rhythm. These three loops are clearly interlocked, and they are the major regulators in many cycling genes. Figure was adapted from Takahashi (2017).

There are multiple benefits to this intricate circadian transcriptional mechanism. Each component of the circadian clock permits cellular physiology and circadian function to be unified and additionally allows circadian timing information to be sent to various non-clock proteins (Figure 1.5; Panda, 2016).

Figure 1.5

Interlocked circadian clocks.



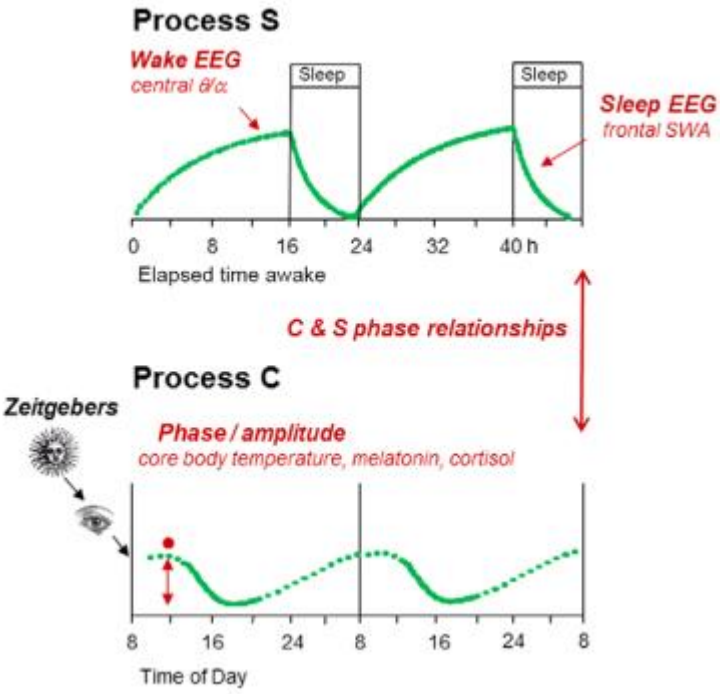
Note. This figure from Oster (2020) shows how the three loops are interlocked and exert their influence by binding to particular circadian specific promoter elements such as ROREs, E-boxes and D-boxes.

1.4 The Homeostatic Drive for Sleep

The sleep/wake cycle is one manifestation of circadian rhythms in humans and other vertebrae. However, this manifestation is impacted by many other factors, including the homeostatic drive for sleep that increases with longer wakening (Borbély, 1982). Borbély proposed a two-process model of sleep (Borbély, 1982; Borbély et al., 2016). Process S was the homeostatic sleep drive and process C was the circadian pacemaker. While the circadian timekeeping system (process C) imposes the underpinning rhythm of around 24 hours, the homeostatic drive for sleep builds up with more time spent awake and reflects the physiological need for sleep (Borbély, 1982). This is regulated by the neurons of the brainstem which are involved in shutting down arousal systems and allowing the brain to sleep (Borbély, 1982; Borbély et al., 2016; Webb & Agnew, 1970). Process S and C are closely connected, and research suggests that clock genes influence the homeostatic component. Animal studies where *Clock* or *Bmal1* have been deleted have resulted in various sleep homeostatic abnormalities (Zaki et al., 2020; see Figure 1.6).

Figure 1.6

The two-process model of sleep.



Note. Figure of the two-process model for regulating sleep timing. This is adapted from Borbéley et al. (2016). The top panel illustrates process S where the homeostatic sleep drive is increasing the longer an individual stays awake. The bottom panel illustrates process C, the circadian arousal, which is higher in the morning and decreases in the evening when the drive for sleep is increasing. These two processes interact to initiate sleep.

1.5 Entrainment of the SCN

The environment displays a rhythmic pattern and synchronising the endogenous clock to this is important. Entrainment describes the synchronisation of the internal biological rhythm (τ) to the earth's daily rotation on its axis (T; Duffy & Wright, 2005). Humans demonstrate an internal period or rhythm of slightly longer than 24 hours, meaning that it requires a daily phase advance to remain in sync with the 24-hour external environment so that physiology and behaviour are timed optimally. In the real world, the biological clock exists in a cyclic environment with several synchronising agents such as temperature, feeding activity, social activity, and light (Roenneberg & Merrow, 2005). The internal biological clock needs to be synchronised or entrained to the 24-h external environment to prevent the rhythm free running. At a very basic level, this process can be conceived as having an input and

output pathway, and an oscillator (Roenneberg & Merrow, 2005). The input refers to the entraining signal, the oscillator generates the circadian rhythm, and the output is the entrained rhythm (Roenneberg & Merrow, 2005).

The primary entraining agent of the circadian clock is light; light is passed directly by the retinohypothalanic tract (RHT) to the master circadian clock where it is detected by intrinsically photosensitive retinal ganglion cells (ipRGCs; Patke et al., 2020). These ipRGCs are rich in the blue-light sensitive photopigment melanopsin (OPN4) which allows them to detect and transduce light (Brainard et al., 2001; Provencio et al., 1998). However, the traditional photoreceptors- rods and cones – also project to the ipRGCs and this light information is relayed to the SCN (Lucas et al., 2012). The rods and cones (extrinsic influence) and melanopsin (intrinsic influence) are the afferent arm of the photo-entrainment pathway (Lucas et al., 2012). Initially it was believed that the ipRGCs alone were responsible for this entrainment, owing to studies that demonstrated entrainment in the absence of these traditional photoreceptors (Paul et al., 2009). However, studies on melanopsin null mice have demonstrated that entrainment remains intact (Panda et al., 2002; Ruby et al., 2002). However, phase resetting responses in these melanopsin knockout mice are reduced by around 40% (Ruby et al., 2002). This all suggests that rods and cones might not be necessary but still play a role in the circadian response to light (Ruby et al., 2002). The precise manner in which they interact with the ipRGCs is unknown (Foster, 2021).

The circadian clock needs to entrain to the external solar day. Interestingly, sunlight changes over the day (Caliandro et al., 2021). Morning and daytime sunlight is characterized by short wavelength blue light (~480 nm) which has a strong impact on the ipRGCS and therefore a strong impact on entraining the circadian clock (Caliandro et al., 2021; Walker et al., 2020). Evening sunlight does not emit the same light and is instead characterized by longer wavelengths (>600 nm) which has minimal effects on the ipRGCs (Walker et al., 2020). The fact that light during the day contains more blue wavelength light and light in the evening contains more red wavelength light is something that the ipRCGs may have adapted to in order to help differentiate between day and night (Walker et al., 2020).

The core SCN receives this stimulation directly and densely projects to the shell SCN (Leak et al., 1999). Gene expression is photically set to only occur at night

in the core SCN. This then passes light information to the shell SCN so that oscillating neurons can be entrained to the external environment. This time-of-day information is then sent in efferent projections to the rest of the brain and peripheral cells around the body. The SCN projects neural and hormonal signals directly to surrounding brain regions and these regions then impact numerous behavioural and unconscious functions all over the body (Leak & Moore, 2001). The coupling of SCN neurons is crucial in this process.

While light is the main entraining agent, non-photic entrainment has been observed in animals and humans (Mistlberger & Skene, 2005; Stephan, 2002). Non-photic entrainment alters behaviour and may also affect the circadian phase of many rhythms including body temperature and melatonin, without the influence of light, and these zeitgebers include physical activity, food timing and social constraints (Patke et al., 2020). The entrainment of peripheral clocks that are metabolically active are impacted by food cues. Food has the ability to alter these circadian clocks without influencing the central circadian clock (Stokkan et al., 2001). All these mechanisms are required to work together to form an optimal phase relationship for good human health and physiological homeostasis (Figure 1.2). Circadian dysfunction in the form of the conflicting internal and external time can have various adverse consequences such as metabolic, cardiovascular, and mental disorders (Patke et al., 2020).

1.5.1 Circadian Period, Phase and Amplitude

Circadian period, phase and amplitude are important aspects of chronobiology and crucial for explaining circadian rhythms and the entrainment of the human circadian clock (Czeisler & Gooley, 2007). The central pacemaker is composed of oscillators that have a genetically controlled *circadian period* (Czeisler et al., 1999). There are several output rhythms under the control of this circadian pacemaker (such as hormones, and core body temperature) which can be measured to estimate the intrinsic circadian period (Dijk et al., 2012). For example, the period could be estimated by measuring the time between DLMO on two successive days. Under normal conditions, these rhythms are entrained to each other, and the external solar day to allow optimal functioning of the circadian clock. As a result, they display specific phase relationships with each other and the light dark cycle (Dijk et al., 2012).

For example, melatonin levels in the plasma peak around four hours before cortisol levels do and around two hours before the minimum in core body temperature.

In the past it was believed that humans had a period of around 25 hours. Aschoff and Wever (1981) carried out seminal studies where participants lived in underground bunkers and recorded periods of around 25 hours in body temperature and other circadian markers. Subsequent cave studies all found similar results but had one main limitation; participants could freely manipulate their artificial light source (Czeisler & Gooley, 2007). When these studies were conducted it was believed that humans were not sensitive to indoor light and with the discovery that this light could phase shift the clock, new methods to estimate circadian period were needed. Forced desynchrony protocols, which have people sleep outside the possible range of entrainment have been utilised to estimate period with a greater degree of precision as they allow an opportunity to extricate the impact of activity related effects and endogenous effects on daily rhythms (Czeisler & Gooley, 2007). Using this technique, individuals have an average intrinsic period of slightly more than 24 hours (24 hours and 11 minutes [24.18]; Czeisler et al., 1999). However, individual differences exist as a period of less than 24 hours was identified in around one quarter of the population. To maintain stable entrainment with the environment, a phase shift of less than one hour every day is sufficient (Czeisler & Gooley, 2007). Individuals with a short free-running rhythm must exhibit a phase delay, while those with a long free running rhythm must exhibit a phase advance.

Circadian rhythms are oscillators, and the phase refers to reference points in the oscillation (i.e., core body temperature minimum or DLMO) and allows for a deeper understanding of period. These reference points facilitate the easy measurement of phase shifts as the change in the timing of this marker can be assessed over two cycles (Czeisler & Gooley, 2007). Under normal everyday conditions endogenous phase is often covered by environmental factors and behaviour. To measure this endogenous phase, constant routine procedures are useful as they limit stimuli that are known to impact the phase markers. The phase of entrainment refers to the relationship between internal and external timing, or, more specifically, the difference between some phase marker as determined by the endogenous circadian clock and the external zeitgeber. This phase relationship depends on several factors including the endogenous period/ τ, the external cycle/ T, the photoperiod (i.e., day

length), zeitgeber strength and zeitgeber amplitude (Czeisler & Gooley, 2007; Roenneberg et al., 2003). Once the circadian rhythm has been synchronised to a zeitgeber, a phase relationship can be observed (Roenneberg et al., 2003). Amplitude can be measured by inspecting a particular marker and measuring halfway between the nadir and maximum value of the rhythm (Roodbandi et al., 2015). The amplitude of a rhythm is indicative of the strength of the circadian rhythm. In the real world, circadian period, phase, and amplitude are intricately intertwined in terms of circadian entrainment.

1.5.2 Phase Resetting

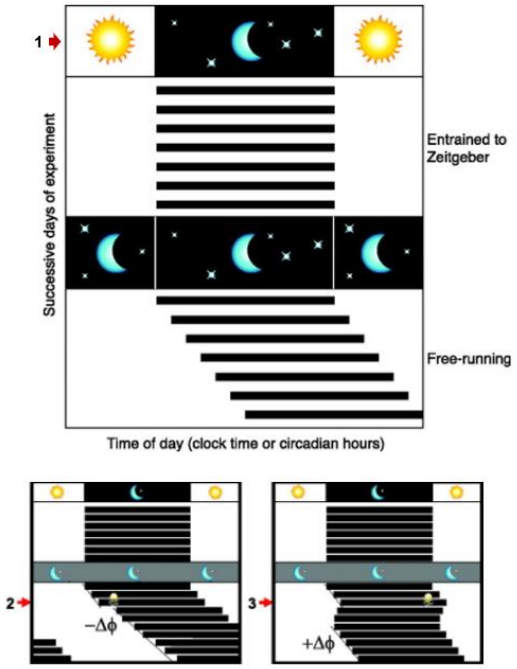
Humans and many other animals display a consistent resetting of their internal timing due to light. A seminal study by Czeisler et al. (1986) demonstrated a 6-h phase delay in body temperature in an elderly woman with a short intrinsic period (23.7 hours), when bright light exposure occurred in the early subjective night. This phase reverted to the normal advanced position 7-10 days after the light exposure was discontinued. Subsequent research by Czeisler et al. (1989) using a constant routine protocol identified phase shifts of up to eight hours in core body temperate minimum when light exposure was centered around the initial core body temperature minimum (CBTmin) in the subjective night. All trials where a substantial phase shift in core body temperature (> 4 hours) were investigated and a similar pattern was found in cortisol levels, suggesting that the master clock controlling both of these rhythms was shifted (Czeisler at el., 1989). The timing of the exposure to the light was the main determinant of the phase shift which highlights an integral property, which is phase-dependent resetting. Both the strength and direction of a phase shift are implicated by the timing of stimulus presentation (Czeisler & Gooley, 2007). The largest phase delays occurred when the light stimulus was administered at the start of the subjective night or the end of the subjective evening (before the CBTmin). To advance the clock, light should be provided late in the subjective night or early in the subjective morning (after the CBTmin), this corresponds to roughly 6am in an individual sleeping from midnight until 8 am. When light was administered in the middle of the circadian day, only very small shifts occurred (Czeisler et al., 1989).

These phase advances and delays in the biological clock can be predicted using the phase response curve (PRC). The PRC describes how the internal circadian

pacemakers are entrained to external day and accurately predict if a system will shift forward, backwards or stay relatively the same (Czeisler et al., 1989; Roenneberg et al., 2003). The critical region of the PRC refers to when light can have its largest effect and falls between the phase delay and phase advance section of the PRC (Jewett et al., 1997). This determines if the individual will have a large type 0 shift or a small type 1 phase shift. However, humans are exposed to light in natural settings outside the critical region and Jewett and colleagues (1997) identified that bright light can cause a phase shift during the subjective day. This suggests that unlike some animal studies where a 'dead zone' was identified, whereby no shift occurred in response to light at a certain point in the day, that humans may have a characteristically different PRC. This is responsive to changes, even near the section of the PRC that phase responses change from advances to delays (Jewett et al., 1997; Pohl, 1982; Figure 1.7; Figure 1.8).

Figure 1.7

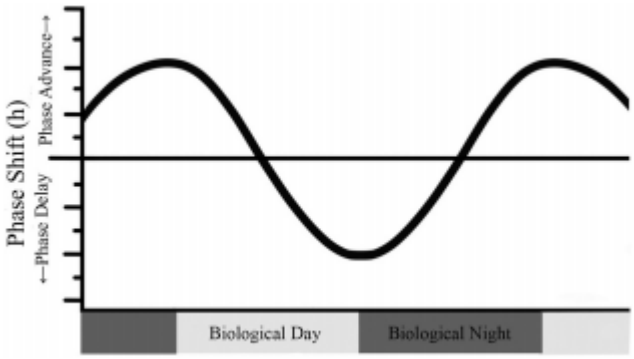
Entrainment of the circadian rhythm to the light dark cycle.



Note. **1.** displays an actogram where locomotor activity and the light dark cycle are entrained; however, when constant darkness is introduced, the rhythm begins to free run. **2.** Displays how light administration in the late evening/early night causes a phase delay. **3.** Demonstrates how light exposure in the late night/early morning causes a phase advance. Figure adapted from Golombek and Rosenstein, (2010).

Figure 1.8

Phase response curve to light.



Note. Taken from Vetter et al. (2021) showing the phase response curve to light. This demonstrates how the degree of phase shifting depends on the individuals' biological timing and on the time of light administration. Individuals' internal rhythm is most often measured by the gold standard marker melatonin, and this is usually higher at night and lower during the day, in humans.

On a molecular level, PER protein levels play a role in determining the phase of the clock (Buhr & Takahashi, 2013). Acute light administration at night when SCN neuronal firing and PER levels are low can increase neuronal firing above the typical firing level during the day. This induces *per1* and *per2* transcription. Light in the late evening/early night delays the behavioural clock, and this is associated with an increase in PER1 and PER2 protein levels in the SCN. Light exposure late at night or early in the morning advances the clock and this is associated with increased PER1 levels (Buhr & Takahashi, 2013).

In terms of phase resetting to light the phase of administration is crucial; however, other physical characteristics of the stimulus in terms of its duration, intensity and wavelength are also important. Further, the ability of light to cause a shift depends on additional factors including the neurophysiology of the mammal (which responds to the light), including its photoreceptor sensitivity and photic history (Vetter et al., 2021). By increasing the dose of light (duration and/or intensity), the resetting of the clock can be increased. Previous research has shown that exposure to light for 6.5 hours in the late evening phase delays the clock. However, the circadian clocks resetting ability may be nonlinear as 12 minutes of bright light exposure has been shown to cause a phase delay of 1.07 hours while 4 hours only delayed the clock by

2.65 hours (Chang et al., 2012). This equates to 12 minutes of bright light exposure resetting the clock by around 5.4 min per minute while the clock was reset by less than 1 min per minute with the longer exposures of 4 hours. The effect of bright light on the clock also seems to saturate between 4 and 6.5 hours (Beersma et al., 2009; Chang et al., 2011). The central message here is that longer light duration causes a larger phase shift, but the relationship is not linear; brief light exposure also has a substantial impact. Light intensity has an impact on phase shifting; generally, with increasing intensities there is a steep increase in the response until a point of saturation is reached (Vetter et al., 2021). However, humans are sensitive to ordinary room light with research suggesting that normal room light (~100 lux) demonstrated half of the phase shift that bright light did, which was 100 times brighter (Czeisler & Gooley, 2007). Research by Gooley et al. (2011) also demonstrated that room light (<200 lux) in the late evening has a profound ability to phase delay melatonin onset irrespective on previous light history.

The photoreceptors that communicate with the circadian pacemaker determine the wavelengths that will have the largest impact. The magnitude of the response to light will also vary based on irradiance i.e., lux (Foster, 2021). Rods mediate night, or very dim vision (Foster, 2021). They can respond to moderate light, but they do saturate (Lucas et al., 2012). Cones can be classed into three different types (short wavelength, middle wavelength, and long wavelength) and mediate colour vision. Cones deal with rapid changes in light intensity and melanopsin is most sensitive to short-wavelength blue light and is more concerned with gradual changes and longer exposure (Foster, 2021; Lucas et al., 2012). Short wavelength light therefore has the greatest phase resetting ability (Czeisler & Gooley, 2007; Lucas et al., 2012). Mid wavelength cones may be important for the initial sensitivity to light as very short exposures to 480 nm light (< 15 minutes) display a smaller response in animals deficient of these cones (Dkhissi-Benyahya et al., 2007). Interestingly, phase resetting also occurs in response to long-wavelength light indicating the role of the long wavelength cones. In the past before artificial light was widely available, the ipRGCs responded strongly the blue wavelength light during the day and showed a minimal response to the longer wavelength red light that sunlight emitted in the evening (Walker et al., 2020). When dark, the moon emitted less than 1 lux of light and the use of candles only emitted around 1 lux at a meter's distance, meaning that this would

have no major effect on the ipRCGs (Gaston et al., 2013; Walker et al., 2020). However, many devices now emit short wavelength light and research has shown that evening use of short wavelength light-emitting eReaders was associated with both a phase delay and suppression of the sleep promoting hormone melatonin (Chang et al, 2015). These unintended biological consequences could have an adverse impact on an individual's long-term health as both behaviour and physiology can be impacted. Depending on wavelength, level of irradiance and duration of exposure the circadian clock will be reset to differing degrees by rods, cones and melanopsin. This is important to consider in daily environments where changes in spectral composition and irradiance may occur (Dkhissi-Benyahka et al., 2007).

The limited work examining the effects of photic history appear to have consistent findings whereby higher levels of previous light exposure reduce the phase shifting effects of later light exposure (Vetter et al., 2021). Chang et al. (2011) displayed that when humans spent three days in dim light (1 lux) and were subsequently exposed to bright light that their phase shifted 40 minutes later than when participants had spent three days in a bright room (90 lux) before being exposed to the bright light. The shift of this subsaturating light around 90 lux after dim light was 1.67 hours, while the phase delay of this 90-lux following on from 90 lux of light was only 1.03 hours demonstrating the impact of photic history. Similar findings were previously reported in Hébert et al. (2002) and Smith et al. (2004). On the other hand, studies which have extended the darkness prior to exposure have observed greater phase shifts in rodents (Refinetti, 2003). This combination of studies all suggests that photic responses can be influenced by prior states of entrainment.

PRCs allow for the accurate prediction of the entrainment of oscillations by examining the relationship between τ and T. Shorter τ generally results in an earlier phase of entrainment (i.e., earlier trough in core body temperature or peak in melatonin rhythm). This has been found consistently in humans and many other organisms. It helps explain why people are more morning orientated; the shorter free-running period means DLMO will occur earlier in their cycle (Duffy et al., 2001).

When the internal period (τ) is successfully entrained to the external period (T), the phase angle is considered to be stable. Stability is impacted when the conditions of entrainment are altered i.e., transmeridian travel and shift work.

Following on from this, the clocks will have to re-entrain which may take several cycles. This phase shifting with shift work, especially with night shift work, may cause feelings of fatigue, insomnia, irritability, reduced performance, and digestive issues (Costa, 2010). If the phase-shift is a once off these usually subside in a few days, depending on some personal characteristics and the duration of the shift. Beyond these short-term effects, many epidemiological studies have suggested that shift work has also been associated with long-term effects on health including gastrointestinal disorders (Knutsson & Bøggild, 2010), metabolic disorders (Pan et al., 2011), cardiovascular issues and cancers (Costa, 2010). The intrinsic period also shortens with age and can cause a phase advance in the elderly (Czeisler et al., 1999). This can have a negative effect on the phase angle of entrainment and may have important roles in understanding the pathophysiology of disrupted sleep among older people (Czeisler et al., 1999).

Changes in sleep wake timing and light exposure have also been associated with amplitude reduction of circadian rhythms in melatonin, core body temperature and cortisol (Dijk et al., 2012). Circadian rhythm amplitude, in general, has also been found to decrease with age. Weaker rhythms are more likely to be phase shifted (Aschoff & Pohl, 1978; Baehr et al., 2000). Reduced circadian amplitude has been associated with increased performance and alertness during the night and an enhanced ability to remain awake. This is beneficial for night shift workers; however, any role it may have in mediating the negative impact that night shift work has on health is unknown (Dijk et al., 2012).

An association in both animals and humans between light-at-night and obesity, impaired glucose control, reduced insulin sensitivity and other markers of poorer metabolic health has been observed and is discussed in further detail in section 1.12 (Vetter et al., 2021)

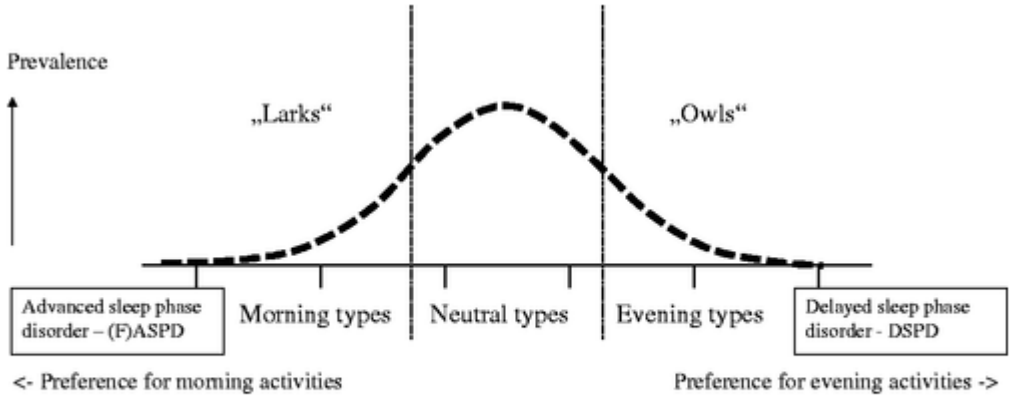
1.6 Defining and Measuring Chronotype

Chronotype reflects an individual's phase alignment with the 24-hour day (Komada et al., 2019). Individual differences in chronotype may result in someone having a propensity to sleep and wake earlier or later in the day, with late chronotypes waking later, reaching peak activity later and sleeping later (Reiter et al., 2021). Chronotypes can differ by up to 12 hours between extreme early and extreme late

types meaning that some people may be going to bed when others are waking up (Figure 1.9).

Figure 1.9

Chronotype distribution in the general population.



Note. Chronotype in the general population taken from Müller and Haag (2017). Most people are somewhere in between the two extremes of being very morning or very evening orientated.

Various ways of operationalising and analysing chronotype have been used over the past few decades. Phase of entrainment can be directly measured by assessing the timing of some biological markers that display circadian rhythms including core body temperature and melatonin. This may involve assessing dim light melatonin onset (DLMO) in plasma or saliva or recording rectal core body temperature (Arendt, 2006; Klerman et al., 2002). DLMO is the gold standard measurement of circadian phase because the master clock in the SCN controls the secretion of melatonin from the pineal gland (Kantermann et al., 2015; Figure 1.1). While laboratory research in the form of controlled experiments has been very informative, these procedures are expensive, labour intensive and require special conditions (Ghotbi et al., 2020; Kantermann et al., 2015).

Different instruments for assessing chronotype in human chronobiology exist with some researchers measuring sleep timing as an estimate for phase of entrainment

(Roenneberg et al., 2003) and others measuring diurnal preference (Horne & Ostberg, 1976). Simply asking people about their sleep timing is a cost-effective method that measures the behavioural analogue of the internal entrained circadian rhythm (Ghotbi et al., 2020). Other measures of chronotype aim to assess intrinsic diunal preference or preferred timing of activities as a measure of chronotype. There are important differences here; namely, estimating phase of entrainment looks at actual behaviours and sleep timing while diurnal preference is more so a measure of intrinsic preference (Leocadio-Miguel et al., 2022).

1.6.1 Questionnaires

Subjectively, chronotype is usually measured by two common surveys, the Morningness-Eveningness questionnaire (MEQ; Horne & Ostberg, 1976) and the Munich Chronotype Questionnaire (MCTQ; Roenneberg et al., 2003). These, however, measure different operationalisations of chronotype. The MEQ measures diurnal preference and rates morningness and eveningness based on individuals preferred timing of activities. Chronotype in this case may be more accurately described as a personality characteristic and lacks a quantitative estimate of actual sleep timing (Roenneberg et al., 2003). The MCTQ estimates phase of entrainment as clock time and allows the interaction between external and internal time to be assessed (Roenneberg et al., 2003). The MCTQ asks simple questions, accompanied by illustrative diagrams about sleep behaviour on work and work-free days. The MCTQ assumes that on a free day, with no work or social obligations, that midpoint of sleep reflects the internal circadian clock while midsleep time on workdays offers a marker of the social clock (Roenneberg et al., 2015). Midsleep time on free days, corrected for any sleep debt accumulated during the week approximates chronotype. This sleep debt is corrected for as individuals often oversleep on free days due to sleep deprivation experienced on workdays (Roenneberg et al., 2015). This midsleep time is a continuous variable and there is no quantitative cut off for early or late chronotype as timing and distribution depends on location, age, and many other parameters (Roenneberg et al., 2015).

The MCTQ is a validated tool for estimating chronotype. Mid-sleep on free days corrected for oversleep has been positively, and strongly correlated with DLMO (r = .68; Kantermann et al., 2015). In the same study, MSFsc came out as the stronger

predictor DLMO when compared to the MEQ measured chronotype. However, at any given score, there was a range of around 4 hours observed between MSFsc and DLMO (Kantermann et al., 2015). It is important to remember that sleep phase can be impacted by more than just the underlying circadian rhythm, namely the homeostatic sleep drive also plays a role, and it may explain why DLMO and MSFsc vary. More recent studies have found a weaker association (r = .35; Reiter et al., 2020, r = .32 Reiter et al., 2021). Notably, the concordance between DLMO and MEQ preference was even weaker (r = -.25, Reiter et al., 2021). While the association between MSFsc and DLMO varies, the questionnaire shows some accuracy and suggests that MSFsc may be a good proxy measure of internal circadian timing (Kantermann et al., 2015; Reiter et al., 2020). Sleep timing and DLMOs close relationship makes logical sense because light exposure impacts DLMO, and sleep prevents light exposure. This association makes it feasible to estimate chronotype in many large-scale studies (Reiter et al., 2020). While the MEQ and the MCTQ are strongly correlated, all research in this thesis that involved primary data collection utilised the MCTQ to assess this interaction between internal and external time.

1.6.2 Sleep Diaries and Actigraphy

Sleep diaries and actigraphy also provide measures of sleep timing. Sleep diaries are based on self-report and actigraphy provides objective estimates. Sleep diaries are often viewed as the gold-standard self-reported measure of sleep duration and provide information on additional sleep related variables (Mallinson et al., 2019). While a high level of convergence exists, some differences have been observed between questionnaires and diaries in terms of reporting sleep duration. Sleep duration is reported as slightly longer on sleep diaries and this may be associated with more insomnia symptoms (Mallinson et al., 2019). Subjective sleep measures have been suggested as an efficient and practicable alternative to some objective measures including polysomnography and actigraphy for collecting information on sleep in community-based samples (Mallinson et al., 2019). Sleep diaries are less time intensive than both objective measures and can provide information on nightly sleep onset latency (SOL), total sleep time (TST), wakefulness after initial sleep onset (WASO), total time in bed (TIB), sleep efficiency (SE), sleep onset (SO), sleep end, midsleep time and sleep satisfaction (Carney et al., 2012). The benefit of a diary over a questionnaire is that it obtains real time, rather than recalled information, on daily

schedule over a predetermined amount of time (Carney et al., 2012). Furthermore, a diary has sleep timing measures over multiple days so allows for the calculation of variability. These measures, however, depend on participants' adherence to complete the diary every day. Research has also suggested that diaries are more precise than questionnaires because participants often reported variables in half hour intervals and tended to round up or down times in questionnaires and this was not observed on diaries (Mallinson et al., 2019). Filling out a sleep diary also has a low cognitive burden as participants only need to remember variables for one night/morning, while questionnaires require more reflection and thought about average sleep cycles (Mallinson et al., 2019).

Actigraphy has been used to measure sleep and wake patterns for years as it can record continuously for 24 hours for many days. Wrist actiwatches have a built-in accelerometer and activity is measured several times per second (Ancoli-Israel et al., 2003). Actigraphy is frequently used in sleep medicine as it provides objective measures of multiple activity and sleep measures including sleep duration, sleep efficiency and sleep onset/offset. This technology can assess when someone is asleep because there is less movement and many devices are available that can measure additional parameters including light exposure (Ancoli-Israel et al., 2003; Roenneberg et al., 2015). One of the main benefits of actigraphy is that it can assess how sleep varies across a given period for individuals in situ. Polysomnography (PSG) is the gold standard for assessing the microarchitecture of sleep but cannot be used over the same time frame as actigraphy or in the individuals' home setting (Jean-Louis et al., 1996). Research has shown that actigraphy is a valid and reliable estimate of sleep and compares well with PSG (Jean-Louis et al., 1996).

From this, using computer technology, an objective measure of midsleep time on all work and free days can be calculated using the same formula as the MCTQ. Beyond sleep data, actigraphy provides information on activity patterns. Non-parametric circadian rhythm analysis can be conducted which generates many key variables that quantify the circadian rhythm (McGowan et al., 2020). L5 is the average activity values during the least active 5 consecutive hours in a 24-hour period while M10 details the average activity during the most active 10 consecutive hours. L5 and M10 onset signifies the time of onset of these periods in the 24-hour day (McGowan et al., 2020). Relative amplitude (RA) is the difference between M10 and L5, which

provides a useful measure of how robust an individual's circadian rhythm is (higher values signifying a more robust circadian rhythm; McGowan et al., 2020). The actigraphy activity data also provides two very important variables around stability and variability over the day. IS indicates interdaily stability and tries to match the 24-hour rest-activity rhythm to the 24-hour light dark cycle (McGowan et al., 2020). Higher values indicate a closer match, more stable rhythms from day to day, and thus good synchronisation (Mitchell et al., 2017). IV indicates intradaily variability and is a measure of rhythm fragmentation (Mitchell et al., 2017). High IV values usually indicate more wake at night and more naps during the day (Mitchell et al., 2017). All these measures can produce a clearer picture of circadian rhythm disturbances. Studying entrained conditions and patterns of wake and sleep may help answer various questions regarding the role of circadian rhythms in health and disease (Roenneberg et al., 2015).

It is important to remember that sleep/wake behaviour cannot be assumed to simply reflect the underlying circadian rhythms but that it is the most explicitly expressed behavioural circadian rhythm (see Figure 1.6).

1.7 The Factors that Influence Chronotype

Chronotype is not static, it changes with age and is influenced by various factors including genetics, gender, and light exposure (Figure 1.10; Roenneberg et al., 2015).

1.7.1 Age & Sex

Chronotype changes with age and these changes are gender specific. During childhood, individuals display an early chronotype which becomes later at age 14 through adolescence (Roenneberg et al., 2004). Based on the MCTQ database, females generally reach their peak lateness at the age of 19.5 while males advance at around 21 years (Roenneberg et al., 2015). Research in a large cohort in the US found a similar trend with females reaching peak lateness before males (around 18 and 19 respectively). However, the advancing of chronotype began earlier on average than in the MCTQ database (Fischer et al., 2017). After this advance, chronotype tends to move toward earlier orientation until the end of life, but the reason for this change with age is largely unknown (Roenneberg et al., 2015). Interestingly, during

adolescence and early adulthood, over half of lifelong chronotype changes occur (Fischer et al., 2017). Generally, women have earlier chronotypes; however, after the age of 21, males advance faster and by the age of 52 catch up with females (Roenneberg et al., 2015). This coincides with the average age that women experience menopause, but it is unknown whether chronotype and this hormonal change are related. In Fischer and colleagues' (2017) research, this differed slightly. Between 20 and 40 males displayed a later chronotype; however, after 40, females were later than males but not later than females under 40. The difference seems to arise from men advancing and women plateauing. Findings from a cross-sectional study in Japan also differed slightly with no difference between males and females regarding chronotype observed in participants between 20 and 50. However, males had an earlier chronotype than females after the average age of menopause (Komada et al., 2019).

While the advance in chronotype differs slightly for genders in different cultures, research converges to suggest that chronotype is advancing for both genders with age after adolescence. Gender differences are not as notable over 50 and chronotype remains advanced with elderly individuals often displaying a similar chronotype to children (Fischer et al., 2017; Roenneberg et al., 2004; Roenneberg et al., 2007). A recent longitudinal study showed for the first time that over a 7-year period that chronotype was advancing slightly with increasing age in all age groups (1 year = 0.66 minutes; Druiven et al., 2021). However, the only significant difference was in those aged 25-29 at follow up, probably due to these individuals being in the stage of peak lateness at baseline. Interestingly, this was observed irrespective of sex. A recent global study did not assess MSFsc but showed that sleep onset and offset at the weekend got progressively earlier as people got older (Jonasdottir et al., 2021).

Furthermore, males show more variability in chronotype than females and while chronotype can still differ largely at any age, older individuals show less variability (Fischer et al., 2017). The reduction in the differences with age are possibly associated with males experiencing reduced testosterone levels (Randler et al., 2012).

1.7.2 Light Exposure

Light, both its timing and the intensity, may be the most influential factor in adjusting the internal rhythm to the external day and plays an important role in shaping chronotype. Chronotype is expected to advance if light exposure occurs in the first

half of the day, predominately in the morning, while the opposite effect is expected if the exposure occurs predominantly in the evening (Roenneberg et al., 2015). The standard phase response curve to light explains this.

Research suggests that chronotype can be impacted by sunlight. Earlier sunrise time as you go further east within the same time zone (northern hemisphere) has been associated with earlier chronotype (Roenneberg et al., 2007). Notably, when the seasons change and the days are longer, chronotype advances (Allebrandt et al., 2014) and during winter months with seasonal changes and more cloud cover, chronotype delays (Kantermann et al., 2007). Later chronotype has also been associated with living further from the equator (Porcheret et al., 2018). Antarctica has an extremely high latitude and provides an interesting setting to examine the impact of light changes in a chronotype dependent manner. Research on Uruguayan students who travelled to Antarctica during the summer demonstrated that when compared to the autumn equinox in Montevideo at home, increased light exposure occurred for all participants in the morning and early evening. Further, between 10 and 12 at night, morning types were exposed to significantly more light than normal. Interestingly, advanced DLMO was observed in evening types and delayed DLMO and sleep onset was observed in early types (Silva et al., 2019). This demonstrates that the circadian clock entrains to natural light and an individual's phase of entrainment may be altered depending on access to natural light.

The impact of light on chronotype can also be observed by examining the impact of lifestyle and light at night. Strong zeitgeber strength was surmised in the past where ancestors were exposed to bright light during the day and no light at night. This led to fewer individual differences in phase of entrainment (Roenneberg & Merrow, 2016). However, in modern society people living and working indoors are exposed to weak light during the day and light at night. This means that they are experiencing a very different light environment than in the past. These weaker zeitgebers will result in a larger phase angle of entrainment i.e., a larger difference between the intrinsic period (τ) and the exogenous period (T; Rémi et al., 2010) and a greater range of phase of entrainment. Papatsimpa et al. (2021) demonstrated that interindividual differences in sleep timing could be reduced by higher daytime illuminance and a knock-on effect of this was smaller chronotype differences in the population. This was noteworthy as it demonstrated how the impact of evening light

exposure was lessened with increased daytime light exposure. This study also demonstrated how average evening light exposure of 35 lux increased individual differences in sleep timing with 20% of people developing an evening chronotype (Papatsimpa et al., 2021). Research from Germany identified that individuals living in small settlements had earlier sleep timing and were more strongly aligned to the light dark cycle when compared to individuals living in larger cities (Roenneberg & Merrow, 2007). Further, evening type individuals taken from their natural environment for two weeks on a camping trip where there was no light other than sunlight, experienced a phase advance (Wright et al., 2013). This is likely due to the different strength of sunlight they are exposed to over the 24-hour day (Caliandro et al., 2021). Interestingly, after the week, all participants displayed a similar chronotype despite having previously displayed a huge range in normal urban life. These studies point toward the importance of strong zeitgebers, such as natural light. In the absence of these strong zeitgebers, for example in urban environments, chronotypes have a larger range (Papatsimpa et al., 2021). Zerbini and colleagues (2021) also compared DLMO in the summer and winter. During the summer, when stronger zeitgebers were present, earlier phase and less variability was observed. This confirmed the effect of strong zeitgebers.

Generally, with more self-reported time outdoors, the strength of photic zeitgeber is increased and chronotype is advanced (Roenneberg & Merrow, 2007). However, research involving a university student population found an association between later MSFsc and more time outdoors (Porcheret et al., 2018). This study identified that later MSFsc was also associated with later sunset times and waking up significantly after sunrise. It is important to remember that many students live different lifestyles, and it is likely that this time outdoors would be in the second half of their circadian day, which would act to delay rather than advance their clocks (Roenneberg et al., 2010). This may also be true for adolescents as this age group generally spends the longest time outdoors and have a later chronotype on average. Further, the entrainment characteristics of the circadian clock may depend on age (Roenneberg et al., 2015).

The impact of light on these behaviours becomes highly apparent when analysing communities with and without access to artificial light. A study on an African town which recently acquired access to electricity and a nearby rural village

with no electricity access reported more evening light exposure, less daytime light exposure, and bedtimes around 1 hour later in the town (Beale et al., 2017). A higher percentage of people living in rural areas also reported a preference for morningness; this preference was also observed in their actions. Rural dwellers tended to rise 35 minutes before sunrise while those in urban areas rose closer to sunrise. Further, individuals in remote areas without electricity reported the highest percentage of morningness, followed by those in rural areas with electricity and then urban area with electricity and modern services (Nag & Pradham, 2012). Electrification status was impacting chronotype as without electricity more people were reporting stronger morning orientation. Among the rubber tapers in the Amazon Forest, those with access to electric lighting showed signs of later chronotypes with later sleep onset times on work and free days. They also demonstrated delayed melatonin onset (Moreno et al., 2015). This is potentially due to a weakening of zeitgebers; those without electricity are likely to have access to more natural light during the day and no light at night. Taken together, these studies demonstrate how in urban environments light exposure is altered and phase may also be impacted.

Differential Responses to Light Exposure. Melatonin is a major sleep promoting hormone released from the pituitary gland which can be suppressed by bright light. However, individuals may vary in their sensitivity to light in terms of melatonin suppression (Higuchi et al., 2005). Some people may have a low sensitivity to light while others may have a high sensitivity to light, and this may therefore impact their bedtime (Phillips et al., 2019). For example, individuals with a delayed sleep phase syndrome (DSPS) display greater melatonin suppression than healthy controls to light exposure (Aoki et al., 2001). This may be impacting their delayed sleep timing. Normal room light of only a few hundred lux also has the ability to suppress melatonin and it is possible that in the general population that those with a higher sensitivity to melatonin suppression have later bedtimes. Research by Higuchi et al. (2005) demonstrated that 2 of their 17 participants displayed no melatonin suppression to bright light and earlier bedtimes which may have been driven by the physiological features of the non-suppression of melatonin (Higuchi et al., 2005). Consequently, it is worth noting that later chronotype may be influenced by sensitivity to melatonin suppression. Furthermore, research has also demonstrated that people with later sleep timing and later MSFsc actually show a heightened intrinsic ipRGC response to blue

light (van der Meijden et al., 2016). The sensitivity of an individual's intrinsic ipRGCs may also influence sleep timing and more specifically chronotype as these individuals with a hypersensitivity to blue light have later sleep timing (van der Meijden et al., 2016).

1.7.3 Genetic Influence

Evidence for the genetic basis of chronotype comes from several lines of research. Genes that influence chronotype include those that directly impact clock genes and therefore the endogenous circadian period and those that impact the pathways zeitgebers use to entrain these genes (Allebrandt & Roenneberg, 2008). Certain findings suggest that chronotype has a polygenetic basis in that the complex phenotype results from several genes all contributing a modest amount (Landolt & Dijk, 2017). Heritability studies have suggested that up to 50% of variation in circadian timing can be explained by genetic factors (Barclay et al., 2010; Kalmbach et al., 2017; Koskenvuo et al., 2007). The genetic influence may be stronger until the end of adolescence and then environmental and social factors have a stronger influence (Adan et al., 2010; Müller & Haag, 2017).

Gene mapping of an extreme sleep behaviour, familial advanced sleep phase syndrome (FASPS) demonstrated that a missense mutation in hPER2, a core clock gene, can change the circadian period by affecting the phosphorylation of the resulting protein (Toh et al., 2001). More specifically, the affected individuals had a S662G mutation in hPER2 on chromosome 2qter while controls did not (Toh et al., 2001). Correspondingly, mouse models with this missense mutation have also demonstrated this shorter period and advanced sleep phase (Xu et al., 2005). These studies, however, only deal with sleep propensity in a sleep disorder and might not be generalisable to the wider population. Interestingly, in the general population, Carpen and colleagues (2005) identified a novel allele PER2 111G which was also associated with morningness. However, not all studies like this have been replicated (Adan et al., 2012).

Genome wide association studies (GWAS) search the entire genome and identify small genetic variations that are more commonly observed in individuals with a certain phenotypic trait. Differences in a single DNA base pair; single nucleotide polymorphism (SNP) are the focus of GWAS studies, and these studies have added

valuable findings regarding the heritability of chronotype. A GWAS study by Jones et al. (2019) identified 351 chronotype-associated loci, in a sample of 697,828 participants. Previous GWAS studies had identified 24 of these loci (Hu et al., 2016; Jones et al., 2016; Lane et al., 2016), however, Jones and colleagues (2019) added a further 327. Some of these variants were observed in or near well documented circadian rhythm genes including *FBXL13*, *ARNTL*, *PER1*, *PER2*, *PER3*, and *CRY1*. Furthermore, in a subset of participants from the UK Biobank with objective sleep measures (N = 85,760), these chronotype-associated loci were associated with objective measures of sleep timing (Jones et al., 2019). Research on the genetic basis of chronotype is constantly growing and although the mechanisms are not fully understood, the underlying biological processes are thought to be influenced by an individual's genetics.

Figure 1.10

The entrainment of the circadian clock.

Note. The internal biological rhythm becomes entrained to the external world by light from the 24-hour solar cycle being passed to the master clock located in the SCN. Chronotype is then shaped by four main components: genes, environment, gender, and age. As a result, individuals tend to be more of a morning 'lark' or a night 'owl'. Diagram from Kelly et al. (2018).

1.8 Circadian System Disruption

Circadian disruption covers several circumstances and is essentially the disturbance of biological timing (Qian & Scheer, 2016). This can range from the cellular to systemic level (Vetter, 2020). Circadian disruption appears to act as an umbrella term whereby circadian misalignment, circadian desynchrony and

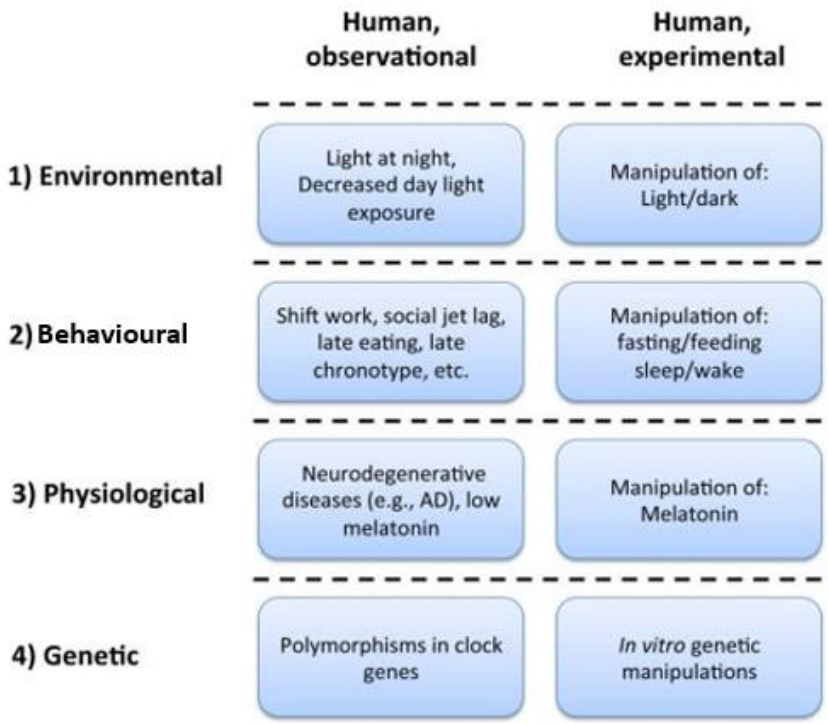
desynchrony are all types of circadian disruption (Vetter, 2020). Briefly, circadian desynchrony and desynchronisation refer to two or more rhythms with different periods. Alternatively, circadian misalignment refers to two or more rhythms with an abnormal phase angle. Notably, the rhythms can be internal or can be a combination of internal and external (Vetter, 2020).

Circadian disruption has been shown to occur at four different levels. Firstly, circadian disruption can occur at a systemic level whereby environmental cycles ("environmental misalignment") or behavioural cycles ("behavioural misalignment") are misaligned relative to the master clock of the SCN (Qian & Scheer, 2016; Figure 1.11). On the other hand, the central clock can be shifted by artificial light at night and the central clock then does not match the behavioural cycle (for example in a hospital setting). Secondly, circadian disruption can occur at an organism level whereby internal misalignment occurs between the central and peripheral clocks. Internal misalignment may also occur between different peripheral clocks in various organs (Qian & Scheer, 2016; Figure 1.11). Thirdly, circadian disruption can occur at a tissue level where desynchronisation occurs between cells in a tissue. Finally, circadian disruption can occur at a cellular level if the phase relationship of clock gene expression is disturbed (Qian & Scheer, 2016). Different levels of circadian disruption occur as a result of different experimental approaches and observations (Figure 1.11). Nevertheless, it is important to appreciate that these may result in different metabolic consequences via different metabolic pathways (Qian & Scheer, 2016).

Modern society promotes a 24/7 environment where individuals can travel, socialise, and work during the body's biological night when the endogenous circadian clock is promoting sleep. This can result in some form of circadian disruption, which in general can be viewed as a stress factor and has been associated with many negative health outcomes including metabolic disorders and psychological problems (Shields, 2002; Vetter et al., 2015; Wittmann et al., 2006). Examples of the modern day causes of circadian disruption include social jetlag, shift work, and jetlag. Circadian disruption is often linked to electric lighting (Figure 1.11).

Figure 1.11

Methods of studying the effects of circadian disruption in humans.



Note. **1.** In human observational studies, environmental light needs to be considered. In experimental studies, light dark cycles are often manipulated. **2.** In human observational studies, lifestyle factors that lead to circadian disruption (i.e., shift work and SJL) are often studied. Specific behavioural cycles are sometimes manipulated in human experimental studies to cause a misalignment with the central clock. **3.** From a physiological perspective, the importance of melatonin is considered. Peschke et al. (2006) observed that patients with type 2 diabetes (T2D) had lower nocturnal melatonin levels. T2D is discussed in further detail in section 1.10. Experimental approaches to alter the circadian system sometimes administer melatonin or suppress endogenous melatonin (e.g., via Bright Light Therapy). **4.** Circadian clock function in humans is hard to decipher. Researchers study polymorphisms in clock genes and carry out genetic manipulation of human tissues in vitro. The molecular clock has been studied with genetic mutations of core clock genes in rodent models, but this is not possible in human studies. Figure adapted from Qian and Scheer (2016).

1.9 Social Jetlag (SJL)

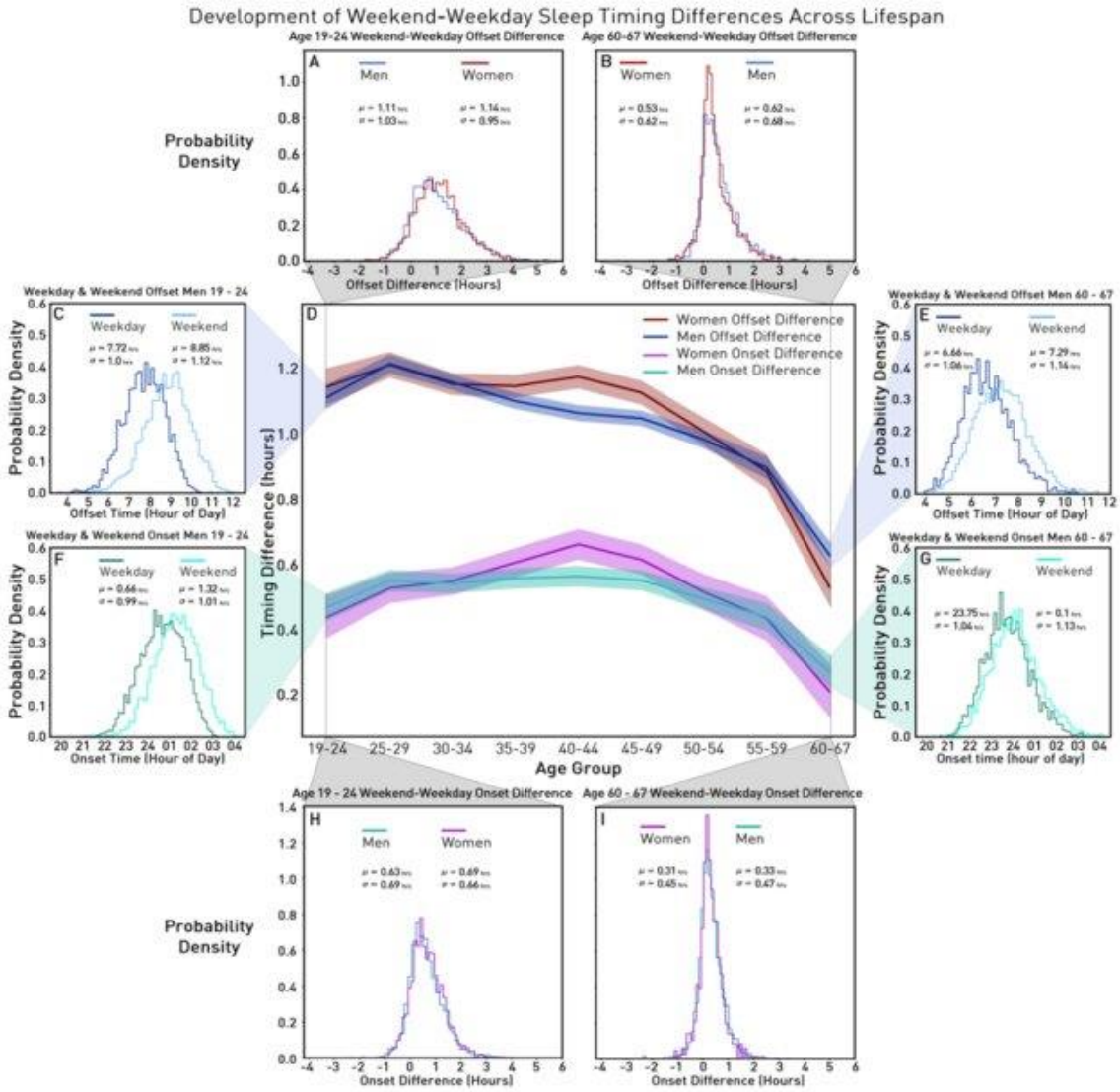
SJL is a chronic form of circadian misalignment that people can experience for their entire working lives and throughout retirement (Garefelt et al., 2021). SJL results from the displacement of sleep timing on work and work free days and the term SJL originated from the transient misalignment associated with transmeridian travel (Wittmann et al., 2006). Jetlag, more generally, only affects a small percentage of the population and has a limited effect while SJL can be like travelling between time zones at the beginning and end of each work week (Roenneberg & Merrow, 2016; Wittmann et al., 2006). While SJL was coined from the more transient travel induced 'jetlag', different forms of circadian disruption may be occurring in both cases (Tavares et al., 2020). With travel induced jetlag, an individual's internal biological clock is misaligned with respect to the external day and environment signals (Vetter, 2020). With SJL, on the other hand, behavioural misalignment occurs whereby social and work schedules are causing behaviours such as feeding/fasting and sleep/wake to be misaligned relative to the internal circadian clock (Vetter, 2020). SJL has a specific quantifiable definition that is calculated by subtracting the midpoint between sleep onset and offset (midsleep) on workdays from midsleep on free days. The absolute value is usually investigated in terms of the consequences of SJL (Roenneberg et al., 2012). However, Roenneberg et al. (2019) recently deduced that there may also be value in examining SJL in its relative form, which can include negative values. SJL can be measured in similar ways to chronotype through self-report of sleep timing via the MCTQ, sleep diaries or objectively from actigraphy (Roenneberg et al., 2015).

Some research has also assessed weekday/weekend day misalignment when information on workdays were not available (Hashizaki et al., 2015). Some other research has assessed differences in either sleep onset or sleep end timing between week/work and weekend/free days as an indication of SJL (Hu et al., 2020). These measures are valuable and often the only option, but it is crucial that this is clearly stated in studies so no ambiguity about the variables exist. Jonasdottir et al. (2021) recently evaluated changes in sleep onset and offset between week and weekend days across the lifespan as indicators on SJL as they believed that one had more control over these than their midsleep. They discovered that the variability in offset tended to be larger than onset. The average offset was between 55 and 70 minutes later at the weekend in comparison to during the week for those aged 19-55. This decreased to 38

minutes on average for those aged over 55. By way of comparison the average difference in onset was between 25 and 35 minutes for those aged 19-55 and this decreased to 20 minutes for those aged over 55 (see Figure 1.12).

Figure 1.12

The differences in sleep onset and offset between weekdays and weekend days for both males and females.



Note. The top two figures show week to weekend day offset difference in males and females for those aged 19-24 and 60-67 respectively. The middle shows the difference in onset and offset for males and females across the lifespan. The bottom two figures show week to weekend onset difference in males and females for those aged 19-24 and 60-67 respectively. This figure is from Jonasdottir et al. (2021).

More than 80% of the population use alarm clocks on workdays to end their sleep, meaning that their biological sleep offset has not been reached (Roenneberg et al., 2015). Most work schedules commence at or before 9 am (89%), and 83% of these

workers have to wake at or before 7 am despite 77% of them naturally sleeping until at least 8 am (Roenneberg et al., 2015). This, in general, results in insufficient sleep on workdays and then oversleeping on free days as a form of compensation (Roenneberg et al., 2015). The opposite occurs for earlier orientated individuals; their social schedule sometimes forces them to stay up into their biological night (Roenneberg et al., 2015). A substantial difference between internal and external timing can result (Roenneberg et al., 2015). At least one hour of SJL has been reported in 69% of individuals while over two hours has been reported in 33% of individuals (Roenneberg et al., 2015). Meanwhile, one study identified that around 6% reported negative SJL (Roenneberg et al., 2013), while another recent study on SJL in Japan demonstrated that, on average, 6.1% of the population displayed negative SJL (Komada et al., 2019). This suggests that their midsleep was earlier on weekend days than weekdays. This statistic does however vary, and many studies fail to provide a description of the negative SJL in the sample, making it difficult to estimate.

SJL allows researchers to quantify weekly circadian misalignment and examine the impact it has on many facets of human health by comparing midsleep on work free days and workdays (Roenneberg et al., 2012). Light exposure is a major cause of SJL (Beauvalet et al., 2017). Due to modernisation and electricity, the way in which individuals interact with their surroundings has changed; most individuals are exposed to on average 50 lux at night after sunset (Blume et al., 2019). Also, working in buildings leads to low light levels during the day which delays the majority of circadian clocks (Blume et al., 2019). This leads to a tendency to sleep and wake later and thus develop more SJL when working early in the morning. This can be visualised by examining societies undergoing differing degrees of industrialisation such as the Brazilian communities investigated by Pilz et al. (2018). Individuals without electricity or who had only recently acquired electricity displayed earlier sleep timing than more urbanised communities (Pilz et al., 2018). Previously these individuals only had access to natural strong zeitgebers during the daytime. The urbanised communities experienced delayed clocks while their social schedules remained relatively the same, resulting in later sleep timing, which may cause more SJL.

SJL and chronotype tend to be highly correlated and peak SJL is also reached when peak lateness is reached (Roenneberg et al., 2019). Accordingly, later chronotypes are often more adversely impacted by social and work commitments

(Komada et al., 2019). Furthermore, SJL decreases with age, possibly due to earlier MSFsc with advancing age (Komada et al., 2019). Among Japanese participants in their twenties, 61% had more than one-hour SJL, while in participants in their thirties, 53.2 % had more than one-hour SJL and in participants in their sixties, only 14.5% did (Komada et al., 2019). SJL also differs between cultures. SJL in a Japanese population was on average lower than in a Central European population (≥ 1 hour 40.1 vs 69% and ≥ 2-hour 11.6 vs 33%; Komada et al., 2019; Roenneberg et al., 2013). Chronotype was also on average 30 minutes earlier. Later chronotypes generally experience sleep loss due to alarm clocks; however, early chronotypes generally suffer due to social pressures to stay awake beyond their biological bedtime (Roenneberg et al., 2013). It is possible that sleep debt also contributes to SJL, with previous research demonstrating a relationship between higher SJL and shorter sleep duration (Almoosawi et al., 2018).

When Wittmann et al. (2006) initially described SJL, it was conceptualised as only impacting people during their working life. This view subsisted, with a lot of research focusing on these cohorts. However, recent research has shown that people still display SJL, albeit to a lesser degree after retirement (Garefelt et al., 2021; Sprecher et al., 2020). Sprecher and colleagues (2020) identified that SJL decreased by roughly one hour when changing from full-time employment to full-time retirement. Garefelt et al. (2021) observed a 40-minute decrease in SJL after retirement. In this research those with a later chronotype had larger SJL changes and those with a partner in full time employment had smaller SJL changes. The reasons for this SJL in retirement are unclear as the same work constraints do not exist. Garefelt and colleagues (2021) suggested that some *"social zeitgebers"* can impact sleep timing among a retired cohort. These *"social zeitgebers"* may include social activities and television viewing. Garefelt et al. (2021) also discussed the concept of *"derived social zeitgebers"* whereby the schedule of an individual's partner may also be playing a role. All of this highlights how a social perspective needs to be adopted when considering sleep as it is not merely an individual phenomenon.

1.10 A Clinical Perspective of Diabetes Mellitus

Diabetes Mellitus (DM) is a complicated and chronic metabolic illness, requiring lifelong monitoring and treatment following diagnosis (American Diabetes

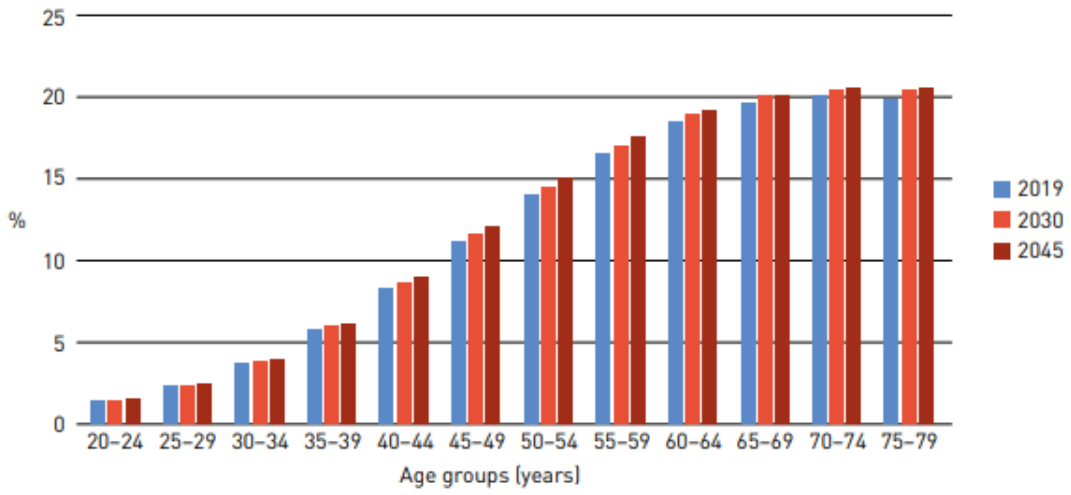
Association, 2020). Diabetes is an umbrella term which encompasses many related disorders with a multifaceted aetiology, but is generally characterised by hyperglycemia (WHO, 2019). Type 2 diabetes (T2D) is the most common form of DM and accounts for 90% - 95% of all cases (WHO, 2019). Specifically, in order to develop T2D, various degrees of beta cell dysfunction are required. Further, T2D is usually characterised by insulin resistance, which indicates impaired insulin sensitivity whereby normal or elevated levels of insulin produce a reduced biological response (Wilcox, 2005). This may also cause disturbances in carbohydrate, fat, and protein metabolism (WHO, 2019). Many people with T2D are also overweight or have obesity which may cause or worsen insulin resistance (WHO, 2019).

Metabolic health has suffered with modern 24/7 globalised society and its associated lifestyle choices and social changes. In recent years metabolic disorders ranging from obesity and metabolic syndrome to T2D have increased in prevalence, reaching epidemic proportions (Karthikean et al., 2019). Nearly 40% of the adult population are currently overweight which increases the risk of developing further metabolic issues (Chooi et al., 2019). Epidemiological studies have shown an increased incidence of T2D since the 1980s (see Figure 1.13). Today, around 9.3% of the global population are believed to have diabetes which is a figure surpassing 463 million cases (IDF, 2019). This is estimated to rise to 578 million by 2030 without sufficient actions (IDF, 2019). It is difficult to accurately capture the prevalence of diabetes in Ireland as no national diabetes registrar exists (Tracey et al., 2015). Research by Tracey and colleagues (2016) identified the self-reported prevalence of T2D among those over 50 years in Ireland to be 8.4%. This study also noted that men reported a higher prevalence than women (10.3% vs 6.6%) and prevalence also increased with age. Those over 75 years of age have the highest prevalence, being 11.8%. This is concerning as diabetes in a major non-communicable disease (NCD), and it is a lifelong condition associated with many secondary complications (Karthikeyan et al., 2019) and the risk of premature mortality (von Schantz et al., 2021). Microvascular complications of diabetes include retinopathy (which can cause vision impairment and blindness), nephropathy (diabetic kidney disease) and neuropathy (damage that occurs to the nerves; Tracey et al., 2015). People with T2D are also at a higher risk of obesity, cataracts, cardiovascular disease, cerebrovascular disease, and peripheral arterial disease which may lead to non-traumatic limb

amputations (Tracey et al., 2015; WHO 2019). The risk of visual impairment in adults aged 50-65 is four times higher in people with diabetes than the general population and the risk of lower limb amputation is 22 times higher (Buckley et al., 2012; Tracey et al., 2015). From 1990 to 2010, there was a 30% increase in disability adjusted life years for people with diabetes, which incorporates number of years lost and number of years lived with the disability (Tracey et al., 2016). This appears to be occurring for two reasons: firstly, due to the increased prevalence and secondly, people with diabetes are living longer (Sinnott et al., 2017). In 2010, it was estimated that diabetes was in the top 15 causes worldwide, and the 10th leading cause in Western Europe of disability adjusted life years (DALYs; Murray et al., 2012).

Figure 1.13

Prevalence of diabetes mellitus in adults ranging from 20-79 in different age groups.



Note. Figure taken from the International Diabetes Federation (2019)

In 2019, an estimated 4.2 million people died from diabetes and its complications; half of these deaths occurred in people under 60 years (IDF, 2019). Mortality due to diabetes is expected to double between 2016 and 2040, and interestingly, sleep disturbances coupled with diabetes increase the risk of all-cause mortality (Foreman et al., 2018; von Schantz et al., 2021). Accordingly, new, and multidisciplinary avenues of research are being investigated to help prevent and manage diabetes. There is huge potential for lifestyle interventions to improve the

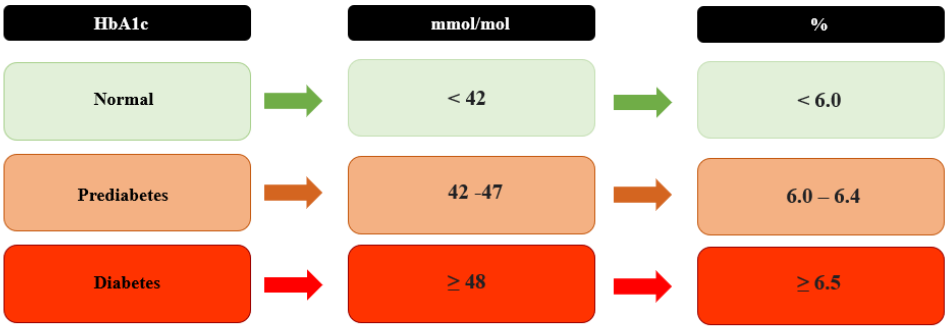
management of T2D which suggests it is not simply a progressive disease. Recent research has also focused on the possibility of remission from T2D (Brown et al., 2021).

T2D symptoms are often not very severe initially, and consequently, diagnosis may not occur straight away, leading to more severe cases upon first presentation (WHO, 2019). This is becoming increasingly problematic as there is an increase in younger people presenting with T2D. Some estimates believe that > 30% of the population have undiagnosed diabetes (WHO, 2019). A diagnosis of T2D clearly has important health implications for individuals. However, beyond the health implications, a diabetes diagnosis may also bring potential stigma that might affect the individual's employment, driving status and health/life insurance (WHO, 2019). There is also a high economic cost to T2D, which is mainly due to the complications arising and the care required. In 2010, it was estimated that 12% of the world's total health expenditure was spent on diabetes, and that this figure was going to continue to rise (Zhang, Zhang et al., 2010). In 2019, in terms of international dollars, diabetes was estimated to cost 727 billion (IDF, 2019).

Glycated haemoglobin (HbA1c) provides an indicator of average blood glucose over the previous 2-3 months (Bennett et al., 2007; WHO, 2011). HbA1c is an effective screening tool and can be used to diagnose T2D (WHO, 2011). Higher HbA1c simply suggests that there is too much sugar in the blood. HbA1c > 42 suggests the presence of prediabetes while HbA1c ≥ 48 suggests the presence of T2D (WHO, 2011; Figure 1.14). People with a diagnosis of T2D need to manage this HbA1c level and ensure levels do not rise too high as this increases the risk of debilitating microvascular and macrovascular complications (WHO, 2011). Furthermore, interventions to reduce HbA1c are effective in reducing complication risk in T2D (Stratton et al., 2000).

Figure 1.14

HbA1c levels expected in healthy individuals, those with prediabetes and those with diabetes.



Note. HbA1c is a measure of glycated haemoglobin. Healthy, prediabetic and diabetic ranges provided here in mmol/mol (IFCC standarisation) and % (NGSP standarisation).

The precise cause of T2D is unknown. However, genetics and lifestyle factors have contributed to this growing epidemic, including rapid social, economic, and cultural changes, ageing populations, dietary changes (which include increases in sugar sweetened beverages, and highly processed foods), changes in the availability of food (making food available 24/7), unhealthy lifestyle behaviours, obesity, reduced physical activity, and increased stress (Gill & Panda, 2015; IDF, 2019; Kelly & Ismail, 2016; WHO, 2019). This has led to individuals eating at any time, even between meals, with research demonstrating that nearly 50% of one sample ate for more than 14 hours each day and less than 10% of the sample ate for less than 12 hours per day (Gill & Panda, 2015). In addition to this shift work, longer working hours and more leisure activities at night have all increased. This may impact sleep duration and quality in addition to timing. Chronotype, and SJL may also influence the risk and management of T2D, and this will be discussed in more detail in section 1.13 and section 1.14. Henson et al. (2020) demonstrated that individuals with a diagnosis of T2D are more sedentary and less physically active than people without the disorder. Interestingly, these behaviours were heightened among individuals with evening chronotypes in comparison to morning and intermediate chronotypes. Notably, while the MEQ was utilised here to categorise chronotype, the categories coincided with earlier and later sleep onset times.

T2D is a chronic condition and the care required to manage symptoms and reduce risks of complications is unremitting (Corbin & Strauss, 1988; Ribu et al., 2019). Treatment for T2D follows a pathway, with the first line of treatment being lifestyle interventions which usually include maintaining a healthy diet, and healthy body weight, smoking cessation, and regular physical activity. Recent research has defined the criteria for T2D remission and different lifestyle interventions, mainly focused on weight loss, are being examined (Brown et al., 2021). If this fails to control blood glucose levels then medication may be administered, beginning in most cases with metformin. In diabetes where the individual may not respond appropriately to insulin or may have inadequate production of insulin, hyperglycemia can be worsened in individuals because gluconeogenesis occurs at an unusually rapid rate. Metformin acts in a variety of ways to suppress hepatic gluconeogenesis and help manage T2D (Melkonian et al., 2020). Combination medication can be administered if this alone is not enough. If this cannot maintain healthy blood glucose levels then insulin injections may be required (IDF, 2019).

T2D is a debilitating disease, but with effective management, monitoring and medication as needed people with diabetes can still live a long and healthy life. Given its substantial burden, and its ever-rising prevalence, it is essential to identify and investigate all adjustable lifestyle factors that may decrease the risk of diabetes among individuals. Ongoing research into prevention and management are therefore necessary to prevent acute complications and lower the risk of long-term complications (American Diabetes Association, 2020). Sleep and circadian rhythms have been implicated in both the risk and management of T2D and evidence that suggests these factors may provide viable avenues for improving diabetes outcomes is growing (American Diabetes Association., 2020). Circadian and homeostatic processes regulate sleep and suboptimal sleep duration and circadian misalignment have increased in recent years due to the 24/7 lifestyle associated with modern society. Public health, particularly public metabolic health, has been negatively impacted by this behavioural factor (Cappuccio et al., 2011; Koopman et al., 2017; Xi et al., 2014).

1.11 Circadian Rhythms and Metabolism

Circadian clocks allow behaviour, physiology, and metabolism to be matched with the most suitable time of the day. The precise mechanism by which the circadian

clock influences metabolic homeostasis is, however, not fully understood. With the light-dark cycle, certain behaviours are timed to either occur during the light or dark phase; the fasting-feeding cycle and sleep-wake cycle are examples of these behaviours. Individuals generally fast at night during the dark phase (while sleeping) and eat during the day when it is bright. In this sense sleep can be viewed as a master switch for metabolism, as the sleep-wake cycle allows the circadian clock to control metabolic processes in the entire body. This influences the peripheral tissues, as they will receive signals from food during the active phase and none while sleeping during the dark phase (Reinke & Asher, 2019). In order for physiological processes to cycle smoothly, cues to the peripheral clock such as food intake, should occur at the appropriate phase; this occurs with circadian alignment (Boege et al., 2021). The SCN is crucial here as it guides these 24-hour rhythms. Two important ways it does this are firstly, by the rhythmic control of melatonin (i.e.) high levels at night to promote sleep and secondly, by signaling the ACTH-cortisol cascade which results in increased alertness in the morning (Panda, 2016). This increase in cortisol is suggested to drive catabolic metabolism. The SCN also signals peripheral clocks to generate system wide rhythms, which, as discussed already, can be influenced by local signals (Panda, 2016). However, even without these local signals (i.e., feeding cues), many metabolic processes such as appetite regulating hormones, energy expenditure and substrate utilisation display circadian rhythmicity. Put simply, this can promote various biological responses at certain times during the 24-hour day. See appendix A for a glossary of some metabolic terms addressed in the coming sections.

1.11.1 Molecular Clocks and Metabolism

The intricate network of 24-hour circadian clocks regulates mammalian metabolism, as it allows for environmental challenges to be met with temporally programmed responses (Reinke & Asher, 2019). Research in different model organisms where clock genes have been disrupted have added some insight into the circadian regulation of metabolism. Previous research converges in suggesting that a system wide loss of circadian clocks leads to a loss of activity and feeding rhythms and can reduce glucose homeostasis (Gopalakrishnan & Kannan, 2020). Turek et al. (2005) demonstrated that *Clock* mutant mice display alterations in fuel metabolism and develop a host of negative metabolic outcomes including hyperglycemia, hyperleptinemia, and hyperlipidemia, that can lead to metabolic syndrome, obesity,

and DM. Further studies in mice have demonstrated that a mutation in *bmal1* has been associated with adipogenesis (Shimba et al., 2005) and impaired glucose homeostasis, with temporal variation of plasma glucose and triglycerides being disrupted (Rudic et al., 2004). Further research by Shimba et al. (2011) identified that mice without the *bmal1* gene had an elevated respiratory quotient value and reduced ability to store fat in adipose tissue. This finding demonstrates how *bmal1* is implicated in fat functioning as an energy store. As a result, there were higher levels of circulating fatty acids and ectopic fat formation in the liver and skeletal muscle which may lead to metabolic syndrome (Shimba et al., 2011). Interestingly, tissue specific *bmal1* deletion did not have the same impact. Glucose intolerance and changes in lipogenic pathways have been associated with *Cry 1 and 2* disruption (Bur et al., 2009; Lamia et al., 2011). Loss of the gene *per* throughout the fruit fly, Drosophila melanogaster, affects lipid metabolism, while loss of *cry* affects carbohydrate homeostasis (Schäbler et al., 2020; Seay & Thummel, 2011). Weakened glucocorticoid and food intake rhythms have been associated with *Per2* knockout in mice, which is problematic as these processes are crucial in metabolism, especially in terms of lipid and carbohydrate metabolism (Yang et al., 2009).

Tissue-specific actions of the circadian clock can also be observed. The liver clock is very important for glucose homeostasis, and it helps balance glucose transport and storage which should match the fasting feeding schedule. More specifically, glucose transport should be lower during the active phase and higher during the resting phase. Deletion of *bmal1* in the liver clock disturbs the glucose transporter 2 (Glut2) which is crucial in this process and results in hypoglycemia during the fasting period (Lamia et al., 2008). Increased body weight has been associated with *bmal1* deletion in adipose tissue (Paschos et al., 2012).

Self-sustained circadian clock rhythms in pancreatic β cells are important for energy homeostasis and glucose metabolism (Sadacca et al., 2011). Mice with a mutation of *bmal1* in pancreatic β cells displayed normal feeding behaviour and activity but defective glucose-induced insulin secretion and glucose intolerance. Similar results were found by Marcheva et al. (2010). *Rev-erbα* may link circadian rhythms and metabolism in peripheral tissues. Studies which down regulate *rev-erbα* in pancreatic islet cells noted a subsequent decrease in insulin secretion and lipid metabolism, with a decrease in the expression of crucial lipogenic genes (Vieira et al.,

2012). Intriguingly, an agonist for *rev-erbα* increased glucose-induced insulin secretion while an antagonist had the opposite effect; it decreased glucose induced insulin secretion (Vieira et al., 2012). Circadian rhythmicity in the insulin regulated glucose transporter (Glut4) and hexokinase (HK), the glycolysis rate limiting enzyme, influences the daily rhythm in insulin sensitivity and glucose levels in circulation. If *bmal1* is deleted from specifically the skeletal muscle, this process is impaired (Dyar et al., 2014).

GWAS studies in humans have also pointed toward clock genes and their roles in metabolism. Variants in *PER3,* for example, have been associated with T2D, while variants in *CRY2* have been associated with fasting glycemia (Below et al., 2011; Dupuis et al., 2010). Candidate gene studies are less robust than these GWAS studies due to reduced replicability and limited sample sizes. However, they have identified an association between T2D and hypertension with two *BMAL1* haplotypes (Woon et al., 2007). Furthermore, genetic alterations in clock genes may influence the development of T2D, metabolic syndrome, and obesity (Scott et al., 2008; Sookoian et al., 2008). Valladares et al. (2015) also suggests that obesity has been linked to eight common clock gene variants.

Beyond circadian clocks influencing metabolism, metabolic signals in the periphery can influence and feedback to circadian clocks in the brain which are important for maintaining the clocks robustness (Gopalakrishnan & Kannan, 2020). A review by Ribas-Latre and Eckel-Mahan (2016) described how many metabolic genes are the target of the CLOCK:BMAL heterodimer, some of which can directly feedback and regulate the circadian clock (e.g. Dec 1 and Dec 2) and others which cannot. The influence of light is, however, very robust and signals from the periphery cannot override this. The peripheral and central clocks may become out of sync. For example, if a nocturnal animal is forced to eat during their biological night (the day), then the circadian expression of the genes in the liver which are rhythmically expressed change.

There is a considerable reciprocal relationship between the circadian clock and cellular metabolism. The molecular clock in implicated in glucose and lipid metabolism as it can separate incompatible metabolic processes and optimise the timing of activities that require more energy. Glucose metabolism begins in the liver where it is phosphorylated to form phosphoglucose. Phosphoglucose then serves in

three different ways. Firstly, glycolysis occurs, and it is used for energy; secondly, glucogenesis occurs where it is stored for further use as glycogen; and thirdly, it plays a role in the pentose glucose pathway (PPP; Panda, 2016). When an organism has eaten, glycogenesis is activated by insulin in response to high glucose levels. This signaling cascade inhibits glycogen synthase kinase (GSK3) and the activity of glycogen synthase (GS) is released. Notably, phosphorylation and activity of GSK3 varies rhythmically and this can influence some core clock components including *REV-ERB* (Yin et al., 2006).

One key regulator of metabolism linked to the circadian clock is the oxidised form of NAD (NAD^+) as this has been shown to have a 24-h rhythm (Nakahata et al., 2009). NAD^+ is synthesised either from simple molecules in the organism anew or nicotinamide phosphoribosyl transferase (NAMPT), a rate limiting enzyme which can catalyse nicotinamide. NAMPT displays circadian expression which is controlled by CLOCK:BMAL1 (Nakahata et al., 2009). NAD^+ has a very short half-life and the salvage pathway is required in order to maintain its availability. Interestingly, daily rhythms in NAMPT and resulting cellular NAD^+ levels are driven by the core circadian clock machinery (Nakahata et al., 2009; Ramsey et al., 2009). Further, PARP1 which is a protein coding gene, uses NAD^+ to increase CLOCK/BMAL affinity to DNA which slows down the PER/CRY complex repression (Panda, 2016). This is important as sudden changes in eating time are less likely to impact the liver clock (Asher et al., 2010).

Sirtuin 1 (SIRT1; *a NAD^+ dependent protein deacetylase*) has been shown to act on the transcriptional regulatory proteins which control metabolism (Asher et al., 2008). Asher and colleagues (2008) demonstrated that SIRT1 expression is under circadian control and is needed for high amplitude clock gene transcription in various core clock genes including *bmal1*, *per2* and *cry1*. SIRT1 has an effect on the molecular clock by binding to CLOCK:BMAL1 in a circadian manner, leading to a breakdown in PER2 (Asher et al., 2008). SIRT1 provides an important connection between cellular metabolism and the circadian clock that can be partially explained by SIRT1 being NAD^+ dependent. Diet can influence rhythmic cellular activities. Decreased cellular activity during fasting increases AMPK phosphorylation, which in turn increases processes like fatty acid oxidation to form ATP. AMPK then interacts with SIRT1 and exerts its effect on the molecular clock. SIRT1 and SIRT6 both act to

deacetylase proteins (*changes the structure of a compound by removing acetyl*) and these are important for temporally controlling metabolism. SIRT1/SIRT6 play a role in chromatin modification and ultimately alter gene transcription. Within the liver, the transcriptional timing of genes involved in peptide and cofactor metabolism are targeted by SIRT1 while the transcriptional timing of carbohydrate and lipid metabolism are targeted by SIRT6 (Masri et al., 2014). NAD^+ is either consumed as a substrate when SIRT proteins deacetylate the target proteins, as discussed above, or, alternatively, NAD^+ can bind to SIRT proteins. This prevents target proteins from being deacetylated and these target proteins can include clock components and many metabolic enzymes (Panda, 2016). In a fed state, different pathways are activated to stimulate anabolic processes such as protein synthesis which can be activated by target of rapamycin (TOR) signaling. The TOR pathway influences GSK-3β phosphorylation and provides another link to the molecular clock as GSK-3β influences PER stability and period length (Zheng & Sehgal, 2010). The requirement of AMPK for high amplitude clock gene signaling during fasting and the role of TOR signaling in period length demonstrate how closely the circadian system, metabolic signaling and diet are related.

The reciprocal relationship between circadian clocks and metabolism suggests that eating patterns, food quality and food quantity impact diurnal rhythms and whole-body physiology (Panda, 2016).

1.11.2 Diurnal Physiology of Metabolism - Circadian and Behavioural Rhythms

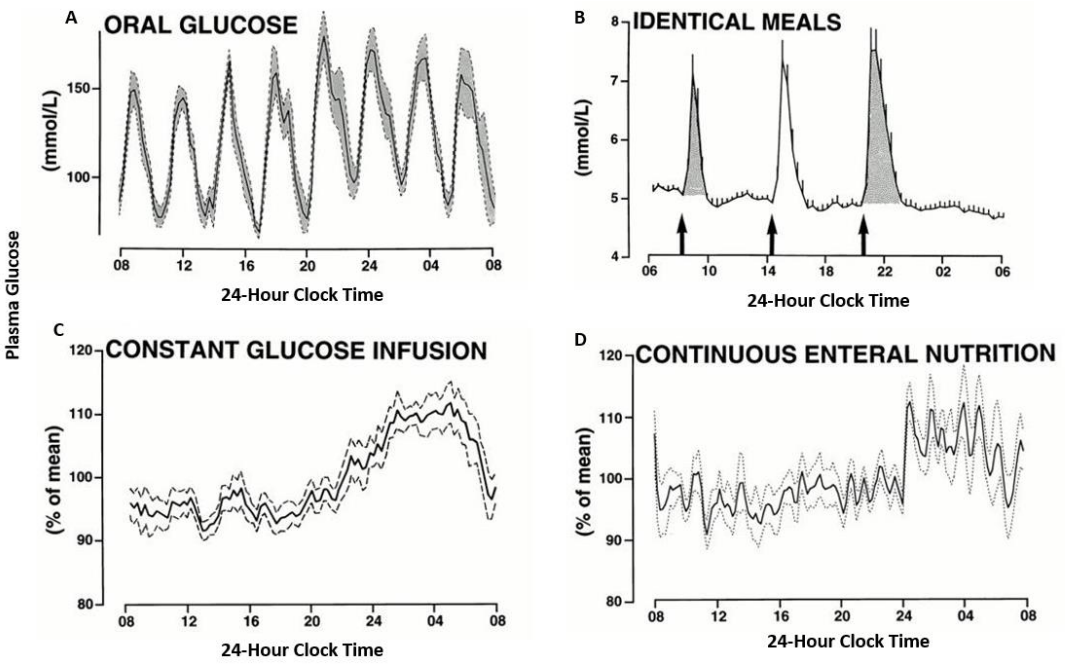
Many important metabolic factors display circadian rhythmicity independent of behavioural schedules, which further highlights the intricate relationship between circadian clocks and metabolism. After consuming a meal, a temporary rise in blood glucose occurs and this is an indicator of metabolic health. This can be viewed as a behavioural response as it is occurring in response to food intake. However, the physiological response to nutrient availability varies over the 24-h day and this time-of-day influence on postprandial glucose can be observed by comparing the rise in glucose after breakfast, lunch, and dinner in healthy individuals (Van Cauter et al., 1997).

In healthy adults, glucose clearance and tolerance are highest in the morning and decrease throughout the day (Poggiogalle et al., 2018). This was deduced from the

highest rise in glucose being observed after dinner, the meal consumed latest in the diurnal rhythm. This has also been observed when participants had the same meal at different time points and observing the glucose response (Van Cauter et al., 1992). The response to the same meal at dinner time produced a response that suggests the meal was twice as big (Figure 1.15B). Research has also shown that if glucose tolerance is tested across the day that responses are higher in the evening and first half of the night than the second half of the night or the morning (VanCauter et al., 1997; Figure 1.15A). Furthermore, one study observed that if individuals are given a constant glucose infusion for one full day and night cycle (24-hour period) that glycemia rises at night and falls in the morning (Panda, 2016; Van Cauter et al., 1997; see Figure 1.15C). Bo et al. (2015) observed delayed and bigger glucose responses and insulin increase to evening meals which was independent of the behavioural cycle. Similarly, with continuous enteral nutrition plasma glucose levels have been shown to increase in the early afternoon and evening and this continues until bed (Van Cauter et al., 1997; Figure 1.15D). This has been observed despite constant caloric intake. The endogenous rhythm of glucose generally results in peak levels occurring during the biological night (Scheer et al., 2009). This discovery is important for understanding how meal timing beyond content is very important for metabolic health (Panda, 2016).

Figure 1.15

Blood glucose changes over a 24-hour period in response to oral glucose (A), three identical meals (B), constant glucose infusion (C), and continuous enteral nutrition (D).



Note. **A**. tested glucose tolerance every three hours across a 24-hour period. **B** looked at response to three identical meals, including 43% carbohydrates, at three time points across a 24-hour period. The area under the curve in the evening was twice as large as the area under the curve in the morning. **C** examined the response to constant IV infusion and **D** examined the response to constant caloric intake through enteral nutrition. These responses are in healthy participants. Figure adapted from Van Cauter et al. (1997).

In sum, among healthy adults the circadian variation in glycemic control results in poorer glycemic control in the late evening and at early part of the night (Poggiogalle et al., 2018). Insulin secretion and sensitivity are also higher in the morning than at night (Serin & Acar, 2019). Notably, among people with obesity and diabetes the glucose tolerance rhythm can differ (Walsh & Wight, 1975). The dawn phenomenon, which is sometimes observed in people with T2D is useful for demonstrating how glucose metabolism is impacted by circadian rhythms (Serin & Acar, 2019). One study identified that glucose stopped decreasing in the evening and rose during the night until its maximum level was reached in the morning (Shapiro et al., 1991). In normal functioning, hormones such as growth hormone antagonise

insulin during the night which corresponds with the lowest levels usually being recorded between 3 and 5 am (Serin & Acar, 2019). Healthy individuals counteract this by secreting more insulin. However, in people with T2D insulin release is often disrupted, and it may not be possible to alleviate the influence of the growth hormone (Serin & Acar, 2019). A pathologic circadian rhythm may result, and this leads to hyperglycemia in the morning. It is unclear whether the delayed or reduced rhythms among people with obesity and diabetes are the cause of consequence of the metabolic disease.

Animal research has also added to the role of circadian clocks in glucose uptake. Among SCN intact animals, glucose uptake was highest at the beginning of the active phase and lowest at the end of the active phase (la Fleur et al., 2001). However, animals with a lesioned SCN showed no variation in glucose tolerance (la Fleur et al., 2001). This may be one way that the biological clock gets the individual ready for the active period. In addition to this, the three major transporters of sugars: SGLT1 (sodium-dependent glucose transporter 1), GLUT5 (the glucose transporter 5), and GLUT2 have demonstrated circadian variation (Hussain & Pan, 2015). Research in mice has shown that mRNAs for these transporters showed peak levels just before the anticipated time of food availability (Iwashina et al., 2011). The hormone insulin is inextricably linked to glucose regulation but evidence for circadian variation is not as concrete. Scheer and colleagues (2009) identified no circadian rhythm in insulin while Chua and colleagues (2013) identified large interindividual fluctuations in insulin making a group rhythm difficult to identify. Glucose and insulin have also been demonstrated to vary across the daily behavioural cycle. These both varied according to meals and decreased at night when the individual was asleep (Scheer et al., 2009).

Hunger displays a large endogenous circadian rhythm with the trough observed in the biological morning and peak observed in the biological evening (Scheer et al., 2013). Ghrelin is an orexigenic hormone, which has been implicated in the regulation of food intake and energy expenditure (Qian, Morris, Caputo, Garaulet et al., 2019). Under normal conditions, active ghrelin levels are predominantly controlled by nutritional status as they decrease after food ingestion and increase when fasting (Qian. Morris, Caputo, Garaulet et al., 2019). During fasting some research has reported a clear circadian rhythm in endogenous active ghrelin (Espelund et al., 2005). Higher levels of active ghrelin have been reported in the biological evening than morning

(Qian, Morris, Caputo, Garaulet et al., 2019). Conversely, a recent review evaluated evidence to suggest that ghrelin did not have a circadian rhythm, so this research is mixed (Poggiogalle et al., 2018).

Leptin on the other hand is an anorexigenic hormone, secreted primarily from adipose tissue, which has also been linked to the regulation of food intake and energy expenditure (Boege et al., 2021). Under normal conditions, leptin is heavily influenced by the behavioural cycle; however, over a 24-hour period, leptin naturally oscillates independent of feeding cycles. Some research has demonstrated that sleep and circadian rhythmicity both influence leptin secretion which increases in the late evening and peak levels occur two hours before light onset (Hsuchou et al., 2013; Simon et al., 1998). Additional research has shown that leptin peaked at the onset of sleep after the last meal and was lowest around breakfast (Scheer et al., 2009). Conversely, other research has failed to identify a circadian variation in leptin levels, suggesting that it is either dependent on the behavioural cycle alone or that circadian rhythmicity in leptin may have been masked by the large meals used in their forced desynchrony protocol (Scheer et al., 2009). Leptin has been demonstrated to entrain to meal timing with one study showing that a 6.5-hour shift in meal timing was associated with a 5–7-hour shift in leptin levels (Schoeller et al., 1997). Generally, with leptin administration, feeding is decreased in humans and rodents unless someone is leptin resistant (Arble et al., 2011). Further, leptin is also linked to insulin and plays a role in glucose homeostasis (Klok et al., 2007; Paz-Filho et al., 2012). Leptin inhibits insulin biosynthesis and secretion from the pancreas while insulin stimulates leptin secretion from adipose tissues (Amitani et al., 2013). Leptin may help reduce insulin resistance (Paz-Filho et al., 2012). Rhythmic leptin levels are lost when the SCN is ablated, suggesting the biological clock control of sympathetic input is crucial (Kalsbeek et al., 2001).

Research is ongoing into the circadian regulation of macronutrient absorption. Diet induced thermogenesis describes an increase in energy expenditure following a meal and this is higher after a meal in the morning than the evening, suggesting less calories will be burned after an evening meal (Bo et al., 2015; Morris, Garcia et al., 2015). This points toward energy expenditure displaying circadian variations. Beyond the transcriptional level, an examination of the human metabolome of blood plasma and saliva demonstrated that in addition to this, 15% of metabolites exhibit a circadian

profile (Dallman et al., 2012). In saliva, the majority of the metabolites exhibiting a circadian profile were amino acids which peaked at various times during the day. In plasma, fatty acids exhibited a circadian profile, generally peaking around the subjective "lunchtime" (Dallman et al., 2012). Research by Chua and colleagues (2013) identified that circadian variation occurred in 13% of lipids studied. Most of these were glycerolipids including diglycerides and triglycerides. Triglycerides were rhythmic at both a group and individual level with peak levels occurring in the morning (Chua et al., 2013). Notably, there was a very large range in the phase of many lipid rhythms which suggests that distinct circadian metabolic phenotypes may exist (Poggiogalle et al., 2018).

Further research has shown that many other hormones and enzymes implicated in metabolism vary over the 24-hour day (Méndez-Hernández et al., 2020). The liver displays rhythmic gene expression in around 20% of protein coding genes under normal conditions (Panda, 2016). This is advantageous as incompatible biochemical processes can be separated. In addition to some liver transcripts displaying circadian rhythmicity, it is logical that some rate-limiting enzymes involved in glycogenolysis and gluconeogenesis, and regulators in metabolic pathways also display daily rhythms (Panda, 2016; Zhang, Liu et al., 2010). Generally, the components of these pathways which are rhythmically expressed anticipate metabolic need and peak levels occur accordingly. This ensures that enough glucose can be found in circulation when an individual sleeps by restricting metabolic processes during the resting period (Zhang, Liu et al., 2010). The regulatory mechanism and metabolic state are integrated as circadian clock components are often influenced by rhythmic metabolites (Panda, 2016). Furthermore, key clock components are also influenced by posttranslational modifiers including kinases and phosphates, which are also crucial for regulating important enzymes in metabolic pathways (Panda, 2016).

This all suggests that there is a strong link between metabolism and the circadian system, with various biochemical and metabolite concentrations showing a predictable rhythm in concentration levels under endogenous control (see Figure 1.16). These rhythms can impact health and negative outcomes may occur if behaviours are mistimed in relation to these endogenous processes. While there are clear, yet distinct circadian and behavioural impacts on these markers, it is important to remember these happen simultaneously and their interaction is crucial for

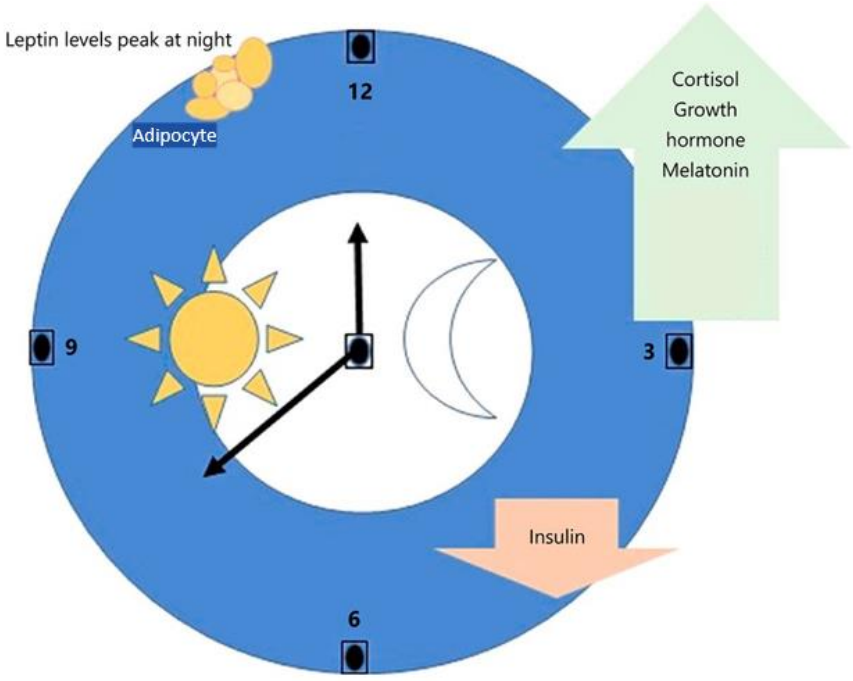
understanding an appropriately aligned day and a misaligned day. Normal circadian physiology is maintained by constant daily patterns of eating and fasting which occurs due to interactions between the internal circadian clock and external timing cues. Frequent disruptions to this may predispose individuals to metabolic diseases.

Neurohumoral Regulation of Metabolism. Melatonin has an important role in metabolic regulation and food intake as animal research has demonstrated how orexigenic hormones are inhibited and anorexigenic hormones are stimulated by melatonin (Piccinetti et al., 2010). Melatonin is also involved in blood glucose regulation, highlighting the role of the circadian rhythm in metabolic regulation (Tan et al., 2019). Notably, the two melatonin receptors (MT1 & MT2) are also located in pancreatic beta and alpha cells, linking melatonin and insulin production/secretion (Bouatia-Naji et al., 2009; Peschke & Muhlbauer, 2010). Importantly, light in the late evening can suppress melatonin (Waldhauser & Dietzel, 1985) and disruption of melatonin by light may therefore result in metabolic disturbances (Cizza et al., 2011). A gene (MTNR1B) which plays a role in encoding one of the melatonin receptors MT2, has been linked to abnormal glucose metabolism and risk of T2D (Tan et al., 2019). MTNR1B activation can cause hyperglycemia as it inhibits the pancreatic beta cells from releasing insulin in response to glucose (Mulder et al., 2009). Many people carry a common variant in the MTNR1B gene (rs10830963), and this seems to strengthen melatonin's inhibitory effect (Tan et al., 2019). Sparsø et al. (2009) found that individuals with the intronic variant of MTNR1B had an odds ratio of 1.6 of displaying impaired fasting glucose. Within this sample, increased odds of T2D were observed in the French and Dutch case-control group. Langenberg et al. (2009) also found a link between this variant and many adverse cardiometabolic markers in healthy participants including higher fasting glucose levels, decreased early insulin response and reduced beta cell glucose sensitivity. Notably, offset of DLMO is delayed in these individuals and this raises the risk of hyperglycemia in the morning when consuming breakfast. This may in part explain why people with this variant are at increased risk of T2D (Lyssenko et al., 2009; Sparsø et al., 2009). Bouatia-Naji et al. (2009) also identified a link between polymorphisms in this melatonin receptor and increased risk of diabetes. Interestingly, McMullan et al. (2013) conducted an epidemiological study and linked diabetes development and low nocturnal melatonin secretion. Women in this study with the lowest melatonin secretion displayed an

incidence of T2D of 9.27 per 1000 while those with the highest displayed an incidence of 4.27 per 1000 (McMullan et al., 2013). This led to suggestions that melatonin may be a potential target to reduce the risk of diabetes. Recent research by Garaulet et al. (2022) observed poorer glucose tolerance among those who had a simulated 'late' meal than an 'early' meal, and greater impairment was observed in MTNR1B G-risk allele carriers. This suggests that eating when melatonin levels are high may adversely affect glucose tolerance through decreased insulin secretion and that this may be pronounced if you are a MTNR1B G-risk allele carrier. Interestingly, while this gene variant has been implicated in the risk of developing T2D, recent research suggests that it is not associated with mortality among people who have T2D (Xue et al., 2021).

Figure 1.16

The daily rhythm of hormones including growth hormone and melatonin.



Note. Figure shows the diurnal rhythm in many important hormones and metabolic processes. Peak serum leptin levels are observed during the night, peak cortisol tends to occur just before waking, melatonin synthesis and secretion occurs during the dark phase (during the night). Conversely, insulin secretion decreases during the night especially between 3 am and 5 am. Figure adapted slightly from Serin and Acar (2019).

1.12 Modern Day causes of Circadian Disruption and Metabolic Health

1.12.1 Electric Lighting

Electric light has enabled humans to take control over their light environment, resulting in most individuals using light until bedtime despite them being extremely sensitive to light (Cain et al., 2020). In modern society, electric lighting can cause circadian disruption as it often provides too much light in the evening/at night, potentially resulting in no true darkness, and insufficient light indoors during the day (Stevens & Zhu, 2015). In the past, people worked outside during the day resulting in strong light exposure in the first half of the day and very little light at night whereas nowadays in the UK, for example, only 1% of the population work outdoors in the natural light (Foster, 2021). With the electrification of modern society, the prevalence of many diseases including cancer, depression, obesity, and diabetes have increased (Stevens & Zhu, 2015). By 2025, 90% of homes around the world are estimated to have white LEDs and the dominant wavelength of these lights is in the blue light range which melanopsin shows peak sensitivity for (Bauer et al., 2018). Desynchronisation of rhythms throughout the body including sleep/wake cycles, patterns of gene expression and hormone regulation/release may result. Darkness during the night is required to prevent both sleep disruption and circadian disruption. The ways in which electric lighting may cause disease is unknown; however, some potential mechanisms include its non-image forming functions such as melatonin suppression, increased alertness in the evenings and altered circadian gene expression.

Striking differences between light exposure in enclosed environments and unsheltered outdoor environments have been demonstrated with the lux of a typical room reaching 400 or less and the lux of midday outdoors ranging from 10 thousand to 100 thousand depending on cloud cover (Cajochen, 2007). In industrialised societies, it is reported that people spend around 90% of their time in enclosed buildings and as a result the many beneficial effects of natural light may be hidden from them (Cajochen, 2007).

Room light (<200 lux) in the late evening has a profound ability to suppress and shorten melatonin secretion (Gooley et al., 2011). Cain et al. (2020) found that around 48% of homes were sufficiently bright in the evening to cause melatonin suppression by 50%, and 73% of homes were bright enough to cause melatonin

suppression by 20%. There was, however, a huge range of interindividual differences in light sensitivity, with some people being more vulnerable than others to the effects of light. In the most sensitive individuals, all light levels were estimated to cause 50% suppression while in the least sensitive individual, no light levels in the home were predicted to cause 50% suppression. The predicted responses to the average home actually varied from 0-87%. Decreased melatonin production has been associated with negative metabolic outcomes. Recent research by Marqueze et al. (2021) identified that melatonin production was reduced in overweight night shift workers, and that exogenous melatonin administration reduced circadian misalignment as measured by the composite phase deviation by around 20%. Early chronotypes displayed the most circadian misalignment and melatonin administration in this group also reduced body weight, BMI and waist and hip circumference (Marqueze et al., 2021). Melatonin signaling and T2D risk have also been associated in some GWAS (Gooley et al., 2011). It needs to be considered that access to electric light in the evening may impact melatonin signaling and this may somehow influence glucose homeostasis and T2D. This might help explain some of the increased risk for metabolic disorders among those who work during the night. Notably, melatonin suppression responses to electric light at night may be modulated by daytime light exposure. For example, previous research has identified that the suppression of melatonin synthesis was decreased by 15% among individuals who has been exposed to light during the day. More melatonin suppression occurs after a week of dim light in comparison to a week of bright light; however, this study noted substantial individual differences (Chang et al., 2011). Individual differences in light sensitivity may explain some of the individual differences in melatonin suppression to a given light intensity. Polychromatic fluorescent light enriched for the short wavelength spectrum has the strongest ability to regulate melatonin. This study essentially demonstrated that blue enriched polychromatic light, in comparison to light with the same intensity, but with lower emissions of this blue light, caused more melatonin suppression (Brainard et al., 2015).

Research on pre-industrial societies where electricity is not yet available or of limited availability has been very beneficial regarding the association between light and sleep behaviours. Less intradaily variability and strong synchronisation with the light dark cycle was observed in Papua New Guinea pre-industrialisation before artificial light had its impact (Siegmund et al., 1998). A study on rubber tappers in the

Amazon Forest, where only some workers had access to electric lighting, demonstrated that electric lighting impedes the alignment between the natural light dark cycle and the endogenous circadian timing system (Moreno et al., 2015). Interestingly, they also reported shorter sleep duration on workdays than free days (Moreno et al., 2015), suggesting that modernisation may be having an impact on sleep behaviours. These changes in light exposure may impact metabolic health and contribute to the growing worldwide epidemic of obesity. A recent study from south Brazil which examined five groups ranging from rural (no electricity access) to highly urbanised demonstrated that the urban group had significantly higher BMI than the rural group (Constantino et al., 2021). Interestingly, a small to moderate association between higher BMI and both lower light exposure during the day (7 am to 5pm) and higher light exposure at night (1am to 6 am) were observed which are characteristic of urbanisation (Constantino et al., 2021).

Light at night (LAN) is problematic for two reasons. Firstly, as demonstrated above, circadian biology is impacted and secondly, it can promote other ill-timed behaviours such as night-time eating or exercise. This can also cause circadian system disruption. Nocturnal light pollution is increasing and artificial light at night exposure occurs in around 80% of the world's population (Falchi et al., 2016; Kyba et al., 2017). This is concerning as Wright and colleagues (2013) identified that light intensity between sunset and sleep is over twice as high than when compared to natural light alone with a full moons light intensity barely reaching 1 lux. Greater night-time light exposure has been associated with poorer sleep quality, shorter sleep duration, delayed sleep onset/offset times and increased sleepiness during the day (Ohayon & Milesi, 2016). This may be occurring as pineal gland melatonin synthesis is suppressed by night-time light (Gooley et al., 2011). Night-time light exposure is also impacted by many electronic devices which often emit monochromatic blue light. 90% of Americans use technological devices the hour before bed (Chang et al., 2015). Many of these technological devices including smartphones, fitness trackers, e-Readers and tablets all contain LEDs which main wavelength of emitted light is blue (Bauer et al., 2018). This is particularly problematic as retinal ganglion cells are most sensitive to blue light and device use can reduce melatonin synthesis, increase alertness before sleep and interfere with sleep. As a result, sleep onset is delayed and alertness is reduced on the following morning (Brainard et al., 2001; Thapan et al., 2001).

Children and adolescents often use technology and bedtime use has been associated with poorer sleep quality, shorter sleep duration and higher BMI (Fuller et al., 2017).

Findings regarding disease risk in this area are predominantly based on observational epidemiology and are therefore inconclusive. Some research has identified an association between LAN in the home setting and impaired obesity and lipid parameters (McFadden et al., 2014; Obayashi et al., 2013). Those with exposure to LAN reported higher BMI, body weight, waist circumference, triglycerides and LDL cholesterol and lower HDL cholesterol in the multivariate analysis, which controlled for several important covariates. Associations between LAN and measures of glucose control did not remain significant. A recent study which objectively measured light identified an association between higher LAN exposure in the bedroom and both general and abdominal obesity (Xu et al., 2021). Furthermore, obesity prevalence has been associated with night-time light pollution in more than 80 countries worldwide (Rybnikova et al., 2016). LAN has been associated with all of these indicators of poor health; however, LAN is also usually associated with circadian misalignment and poor sleep quality, and it is possible that these are all connected in having this negative impact. More research is required to determine exactly how LAN exerts its effects, but this may be related to the suppression of melatonin associated with LAN. Some animal research has demonstrated that melatonin administration can reduce body weight gain (Terrón et al., 2013) and improve glucose homeostasis in an animal model of diabetes (Agil et al., 2012). The Zucker diabetic fatty (ZDF) rats in this study displayed improved insulin action and beta cell function (Agil et al., 2012).

1.12.2 Shift Work

With modern 24/7 society, night shift work is very prevalent with around 20% of workers engaging in regular shift work (Boivin & Boudreau, 2014; HSA, 2012). Shift workers exhibit drastic circadian disruption due to work schedules during their biological night and evening. Circadian misalignment occurs when the circadian rhythm and the sleep/wake cycle do not match (Figure 1.17). This misalignment causes a disruption to the SCN network rhythm and both sleep and metabolism become disturbed (Kulkarni et al., 2020). This is concerning as less than 3% of shift workers report complete entrainment to night shift work schedules (Folkard, 2008), meaning that the circadian rhythm is constantly being reset.

Compelling evidence from epidemiological literature suggests that metabolic health is adversely affected by night shift work. Epidemiological studies have, for example, demonstrated that night shift work has been associated with obesity, T2D, metabolic syndrome, and glucose dysregulation (Kulkarni et al., 2020; Strohmaier et al., 2018; Szosland, 2010). Research shows that the incidence of metabolic syndrome is higher in shift workers (Kulkarni et al., 2020). This then increases the subsequent risk of diabetes, cardiovascular disease, and stroke. A meta-analysis by Gan and colleagues (2015) identified that shift work history was associated with 9% higher risk of T2D. Interestingly, males, and those who engaged in rotating shift work had a higher risk (Gan et al., 2015). One of the epidemiological studies included in the meta-analysis above showed that rotating shift work in female nurses was associated with greater risk of T2D. The risk increased with more years as a shift worker and body weight seems to moderate this association (Pan et al., 2011). Shift work has also been associated with obesity (Sun et al., 2018). A study of nurses' health indicated that individuals may benefit from a shift schedule that suits their chronotype, as late chronotypes demonstrated the higher risk of diabetes when working daytime shifts and morning types showed increased risk when working rotating shifts (Vetter et al., 2015).

A prospective cohort study of female nurses identified that rotating shift work was associated with risk of T2D, with more years worked associated with higher risk (Shan et al., 2018). In this study unhealthy lifestyle behaviours that shift workers had such as low physical activity and smoking was also associated with higher risk of T2D. Notably, rotating shift work and unhealthy lifestyle behaviours combined were associated with increased risk of T2D (Shan et al., 2018). A review examining the consequences of shift work and insufficient sleep demonstrated that night shift work was associated with weight gain, increased risk of cancers (breast, colorectal and prostate), T2D, stroke, and myocardial infarction (Kecklund & Axelsson, 2016). The risk of these cardiometabolic diseases with shift work was similar to the risk associated with insufficient sleep. It is possible that they have a similar mechanism or that the adverse metabolic consequences are simply attributable to sleep disturbances rather than circadian disruption (Kecklund & Axelsson, 2016). However, the number of studies of shift work and adverse health outcomes, suggests the view that insufficient sleep alone causes poorer metabolic consequences in shift workers is too simplistic.

Some epidemiological studies suggest that shift workers are more likely to smoke, eat more food at night, be less physically active and experience more stress (Kecklund & Axelsson, 2016). One reason for the increased risk of disease with shift work is potentially these unhealthy lifestyle habits or socioeconomic status. However, data is beginning to emerge that contradicts this view. For example, studies have found that night shift workers may exercise more, not less, than the general population (Loef et al., 2018; Loef et al., 2017). Interestingly, circadian misalignment may be an independent risk factor. Some laboratory simulated conditions have been useful in further elucidating the role that shift work and circadian disruption may play in increasing cardiometabolic disease risk. One potential cause is changes that occur in hunger and satiety hormone levels, for example, decreased leptin and increased ghrelin, as a result of circadian misalignment (Boege et al., 2021). Leptin and ghrelin both have a role in energy metabolism and are under circadian control so it is possible that this may be disrupted with circadian misalignment and impact metabolism.

A laboratory protocol over 10 days among healthy volunteers demonstrated that circadian misalignment was associated with decreased leptin, reversed daily cortisol rhythm, increased mean arterial blood pressure, reduced sleep efficiency, and increased fasting plasma glucose. Intriguingly, 3 of the 8 participants' fasting plasma glucose were in the pre-diabetic stage after these 10 days (Scheer et al., 2009). Some research has suggested that the 24-hour satiety hormone leptin may be differently impacted in males and females; in this study females showed a 7% decrease and males showed an 11% increase (Qian, Morris, Caputo, Wang et al., 2019). Females also showed 8% increase in the hunger hormone ghrelin and subjectively reported feeling less full. Males showed no change in ghrelin levels but did subjectively report cravings for energy dense foods which was in contrast to their hormones, suggesting other pathways may be involved (Qian, Morris, Caputo, Wang et al., 2019).

Further research demonstrated that glucose tolerance is reduced by circadian misalignment (Morris, Yang et al., 2015). Insulin sensitivity is also reduced with circadian misalignment which may explain the increased risk for T2D (Boege et al., 2021). Previous research has also suggested an association between circadian disruption and elevated fasting plasma glucose, elevated free fatty acid levels and lower insulin-simulated glucose disposal, which is a proxy measurement of muscle insulin sensitivity (Wefers et al., 2018). This study identified that acute circadian

misalignment was associated with muscle-specific gene expression changes (Wefers et al., 2018). These changes may be tissue specific but may also occur at a circulating level as circadian misalignment has been implicated in the alteration of many plasma proteins that are important for metabolic regulation (Cedernaes et al., 2015; Depner et al., 2018). These laboratory simulations are useful for elucidating the short-term implications of shift work but are not as useful for examining the long-term effects.

Animal studies have demonstrated a reciprocal relationship between circadian rhythms and some hormones. For example, circadian desynchrony can result from diet induced insulin resistance and insulin release can cause a phase shift in circadian clock genes (Challet, 2015; Touati et al., 2017). All of this research, from both field studies and simulated studies, suggests that metabolic health and circadian rhythms are linked, and the impact of shift work led to the idea that weekly circadian misalignment, in the form of social jetlag (SJL), may also impact metabolic health (see section 1.15).

1.12.3 Jetlag

Contemporary lifestyles have brought with it many modern conveniences including jet travel across time zones and the swift shift of the light/dark cycle associated with this (Voska et al., 2010). Jetlag is a transient form of circadian disruption whereby the circadian system and the external environment are out of synchrony. Jetlag causes a desynchrony of the SCN from some of the downstream peripheral clocks and this has many short-term symptoms and long-term implications. The main symptoms of temporary circadian desynchronisation are impaired daytime functioning and greater daytime sleepiness (Voska et al., 2010). Jetlag can also cause various metabolic, cardiovascular, neurological, and psychiatric symptoms while the circadian system is gradually re-entraining (Voska et al., 2010). Other short-term symptoms include impaired performance and functioning, general malaise, gastrointestinal upset, irritability, and changes in mood (Boulos et al., 1995; Walker et al., 2020). While these are usually temporary, they are often disruptive and vary in magnitude depending on travel direction and the amount of time zones crossed (Eastman & Burgess, 2009).

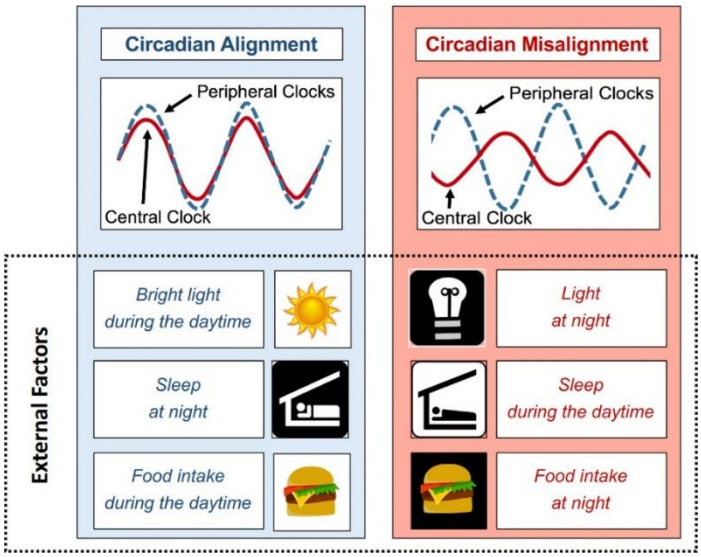
With flying east, the circadian clock must phase advance and while flying west, the circadian clock must phase delay (Eastman & Burgess, 2009). It is harder to phase advance the human circadian clock and therefore re-entraining after flying west is

easier than travelling east (Eastman & Burgess, 2009). Jetlag involves sleep disruption; for example, after travelling east, initiating sleep is difficult after the first night for the following few nights. Interestingly, this is unnoticed on the first night as travelling may cause sleep deprivation and fatigue and sleep can be initiated effortlessly during this period. In contrast, after flying to the west, altered sleep quality lasts for fewer days even if the same number of time zones are crossed. Individuals may experience some problems maintaining sleep; however, this seems to disappear in a few days following travel (Voska et al., 2010). Notably, individual variation in jetlag does exist, with some travelers experiencing fewer symptoms.

Long term health risks are associated with frequent jetlag, and these include increased cortisol levels, cognitive deficits, temporal lobe atrophy and disorders of the menstrual cycle (Cho et al., 2000; Cho, 2001; Iglesias et al., 1980). Notably, after transmeridian travel, behavioural cycles do not match circadian cycles and therefore, food consumption is likely to occur at inappropriate phases and risk of T2D and cardiovascular disease may increase with repeated jetlag (Hampton et al., 1996). Higher cancer risk has also been observed in flight attendants due to regular travel across many time zones (Pukkala et al., 2002; Rafnsson et al., 2001). As the circadian clock is gradually reset to the new time zone, the symptoms of jetlag dissipate. However, the short and long-term effects of jetlag are a clear public health concern (Eastman & Burgess, 2009).

Figure 1.17

Circadian alignment and circadian misalignment between central and peripheral clocks.



Note. Figure from Poggiogalle et al. (2018)

1.13 Chronotype and Metabolic Health

Individuals with an evening chronotype often must shift their weekly schedule by 2-3 hours in comparison to morning type individuals, and their biological night may not be synchronised to the light-dark cycle. Later chronotype has also been associated with unhealthier lifestyle behaviours including smoking and a higher risk of various diseases (Wittmann et al., 2006). There is growing evidence to suggest a potential association between evening chronotype and increased risk of cardiovascular disease and metabolic disorders (Merikanto et al., 2013; Yu et al., 2015). Chronotype has been associated with several physiologic processes that are linked to cardiometabolic health; glucose metabolism, for example, has a circadian rhythm. Glucose metabolism has also been associated with variants in circadian clock genes that have been linked to sleep homeostasis and chronotype (Kalsbeek et al., 2014). Merikanto et al. (2013) identified that evening chronotype in comparison to morning chronotype had 2.3 greater odds of T2D. Yu et al. (2015) in a Korean study found a similar relationship; however, sex differences were evident. In males, there was an association between evening chronotype and T2D, while in females, there was an association between evening chronotype and metabolic syndrome (Yu et al., 2015). A study in the UK Biobank identified increased odds of diabetes among definite evening

types when compared to definite morning types (Knutson & von Schantz, 2018). Tan et al. (2019) identified a similar risk of T2D among definite evening types in comparison to morning types in the UK Biobank. This was identified while controlling for additional variables including sleep duration and blood pressure. Later chronotype has also been associated with poorer glycemic control in participants with T2D (Reutrakul et al., 2013) and prediabetes (Anothaisintawee et al., 2017). These relationships were independent of many other sleep and clinical variables which suggests that the phase of entrainment in everyday life may influence metabolic dysregulation in these conditions.

A relationship between chronotype and BMI has also been previously described in T2D (Brown et al., 2013). One study noted that around 11% of patients with T2D skipped breakfast and these patients had a later chronotype, higher BMI and higher HbA1c than morning type individuals (Reutrakul et al., 2014). Chronotype may influence the timing of dietary intake with research suggesting that fewer and larger meals are consumed by evening chronotypes as they wake later (Dashti et al., 2015; Meule et al., 2012). Participants with later chronotype may be more likely to skip breakfast (Meule et al., 2012) and as a result, have poorer glycemic control. Individuals who skip breakfast generally consume more in the evening and this has been linked to higher BMI, irrespective of chronotype. This could also have an undesirable impact on glycemic control in people who have a late chronotype and T2D (Reutrakul et al., 2014). However, a recent study in the UK Biobank identified very minor variations in HbA1c among individuals with T2D based on circadian preference, which were unlikely to be clinically relevant (Xue et al., 2021). Furthermore, chronotype was not associated with insulin use or odds of attaining a desired therapeutic goal. If this study is replicated, it may suggest that chronotype is not relevant to this marker of diabetes management. However, the authors also suggested that perhaps the circadian misalignment associated with chronotype is a more significant variable which was not accounted for in this study.

A recent study identified how urbanisation appears to lead to later sleep timing, later chronotype and also poorer metabolic and anthropometric variables. Urbanisation and modern society, in this sense, may be a risk factor for these metabolic variables and chronotype may play a role (Martins et al., 2020). This research compared men living in either an urban or rural Amazonian community. Urban dwellers displayed

poorer metabolic and anthropometric variables, later sleep onset, offset and midsleep times on work and free days in comparison to rural dwellers. Urban dwellers had significantly higher body fat and certain other indicators of metabolic risk including glucose levels, insulin resistance, and fasting insulin (Martins et al., 2020). Notably, both communities had access to electricity, but the urban areas had more illuminance and activities outside the home and lower light stimuli during the day due to working inside.

Research has found an association between evening chronotype and increased odds of higher serum cholesterol, LDL cholesterol, lower systolic BP, faster resting heart rate and arterial hypertension (Merikanto et al., 2013). A small-scale German study found an association between higher systolic BP, lower HR variability and evening chronotype (Roeser et al., 2012).

The reason for the association between late chronotype and poorer health is still unclear. Differences in sleep characteristics may explain some of the impact as more insomnia symptoms and poorer sleep quality has been found among evening chronotypes (Lima et al., 2010; Raman & Coogan, 2020). SJL may also play a role as people with late chronotypes generally display more SJL. SJL reflects a form of circadian disruption, and this disruption may be negatively affecting health in later chronotypes (Wittmann et al., 2006).

1.14 Social Jetlag and Metabolic Health

SJL, like later chronotype, has been associated with negative consequences for health and well-being and may contribute to an unhealthy lifestyle (Wittmann et al., 2006). Since SJL is an indicator of chronic circadian disruption and much of our biology is regulated by the circadian clock, SJL may be a chronic physiological stressor. For this reason, it is emerging as a public health concern.

SJL has been associated with numerous unhealthy behaviours including low physical activity (Rutters et al., 2014) and increased odds of smoking (Wittmann et al., 2006). SJL has also been linked with increased nicotine and caffeine consumption (Gabud et al., 2015; Wittmann et al., 2006), lower amplitude in some circadian rhythms, including body temperature (Polugrudov et al., 2016), and increased resting heart rate (Kantermann et al., 2013; Rutters et al., 2014). This increased resting heart rate indicates increased sympathetic stress on the heart and may carry an increased

risk of cardiovascular disease (Kantermann et al., 2013). Greater SJL has recently been associated with poorer dietary intake in undergraduate students (Bodur et al., 2021; Yoshizaki & Togo, 2021). These students consumed less grain and more sugar and confectionaries. Rusu et al. (2021) recently identified an association between SJL and poorer eating habits including snacking late in the evening before bed and watching TV while eating. These dietary choices demonstrates how SJL may be implicated in various lifestyle related diseases. Greater SJL has been associated with more depressive symptoms (Levandovski et al., 2011), poorer self-reported health (Sprecher et al., 2020) and bedtime technology use. More specifically, having a computer or phone in the bedroom and internet access in the hour before bed (Lang et al., 2018).

This adverse behavioural and cardiovascular profile puts healthy individuals with greater SJL at an increased risk of various metabolic, cardiovascular, and endocrine diseases (Rutters et al., 2014). SJL associates with weight gain in a dose dependent manner and with increased risk of obesity (Roenneberg et al., 2012). Bodur et al. (2021) recently identified that students with an hour or more SJL had increased neck and waist circumference and BMI. SJL has also been associated with increased risk of metabolic dysfunction which may result in diabetes or cardiovascular issues (Islam et al., 2018; Parsons et al., 2015; Wong et al., 2015). Research in individuals 61 and younger demonstrated a 2-fold increased risk of diabetes/prediabetes and metabolic syndrome in those with high SJL (Koopman et al, 2017). This was replicated in a Japanese population where an increased risk of metabolic syndrome was associated with SJL (Islam et al., 2018). Notably, this association was significant after controlling for sleep quality, leisure time exercise, alcohol consumption and caloric intake. More specifically, SJL has also been associated with many metabolic abnormalities including higher fasting plasma insulin, insulin resistance, adiposity, dysglycemia, dyslipidemia, excessive inflammation, higher triglycerides, and metabolic syndrome (Wong et al., 2015; Parsons et al., 2015).

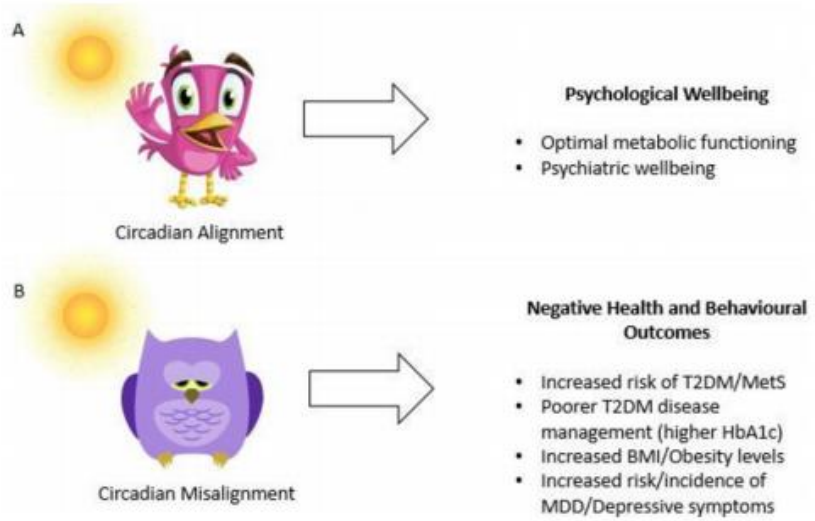
Research by Mota and colleagues (2017; 2021) has been adding to the understanding of how SJL can influence metabolic health. In 2017, Mota et al. identified an association between SJL and risk of obesity and being metabolically unhealthy. Furthermore, among a cohort of metabolically unhealthy obese, an association between SJL and fasting glucose was observed (Mota et al., 2017). Some research has identified an association between greater SJL and higher HbA1c levels

among individuals with type 1 diabetes (T1D; Larcher et al., 2016; Rusu et al., 2019). In contrast to this, some research found no association between SJL and HbA1c among adolescents with T1D. They did identify that those with greater SJL had greater insulin requirements (von Schnuirbein et al., 2018). The association between HbA1c and SJL in T2D has also had some mixed results. One study found an association between greater SJL and HbA1c among a subgroup of metabolically unhealthy obese participants. However, socioeconomic, and smoking status appeared to explain most of this association (Parsons et al., 2015). Other studies have noted a trend toward significance (Reutrakul et al., 2013), while some other studies have found no association (Mokhlesi et al., 2020). Recent research by Mota et al. (2021) failed to find an association between SJL and HbA1c among a cohort with T2D or NCDs more generally. However, it did find an association between SJL and changes in fasting blood glucose over a one-year follow-up among the full sample and a subgroup with T2D. SJL had a negative impact on blood glucose control and resulted in these individuals having a worse metabolic profile. While this study did not find an association with HbA1c specifically it highlights the need to be aware of SJL, especially if glycemic control is already impaired.

There are a multitude of consequences of living against the circadian clock (Figure 1.18). These may be partly due to changes in lifestyle variables including physical activity and different physiological reactions to food intake, depending on what time it is taken at, with circadian disruption promoting food intake at non-optimal times. However, it is difficult to determine causality; the clock could be causing the problem, or the problem may be impacting the clock.

Figure 1.18

The consequences of circadian alignment and misalignment.



Note. **Figure A** shows a morning lark waking up early and going to bed early. This natural wake time reflects the internal clock and optimal function results. **Figure B** shows a night owl forced to get up earlier during its internal biological night, which results in many negative health and behavioural outcomes. Diagram taken from Kelly et al. (2018).

Food timing, beyond caloric intake or macronutrient quality is important for metabolic health and mistimed eating can have negative metabolic consequences (Challet, 2019). In one study, obese Zucker rats were either fed *ad liditum* or only at night (during their active phase) and those fed at night gained less weight, despite a similar amount of food being consumed (Mistlberger et al., 1998). Further research has shown that mice fed during their biological night can phase shift their peripheral clocks by 12 hours while the SCN remains the same (Mukherji et al., 2015). This results in severe circadian desynchrony and has been linked to higher body weight and risk of diabetes and metabolic syndrome (Arble et al., 2009; Mukherji et al., 2015). SJL may lead to later mealtimes which are out of sync with the individual's endogenous preference (Mota et al., 2019; Rusu et al., 2021). Evening consumption of a higher percentage of daily dietary intake has been associated with 80% increased odds of being overweight or having obesity (Xiao et al., 2019). In humans, inappropriately timed food intake or sleep can phase shift peripheral clocks causing

mistiming in relation to the central clock (Wehrens et al., 2017). Further research has shown that if food is consumed closer to DLMO then there is an increased risk of having higher body fat (McHill et al., 2017).

Repetitive misalignment between behavioural and environmental rhythms from the SCN driven circadian rhythm can result in a loss of homeostasis as the peripheral rhythms may become out of sync (Boege et al., 2021). Alterations to the systems involved in maintaining energy homeostasis by regulating hormones involved in hunger and satiety may be influenced. For example, Rusu et al. (2021) demonstrated that acetylated ghrelin levels were higher among those with SJL in comparison to those without SJL. SJL may also interact with the hedonic control of food intake. Nechifor et al. (2020) identified increased activity in brain areas involved in reward processing and cravings among people with SJL in comparison to those without SJL. Rusu et al. (2021) found an association between SJL and increased appetite for energy dense food and this suggests that ingesting these foods may be linked to the anticipated pleasure. Typically, this food is higher in fat and less filling which again increases obesity risk and ties in with the associated brain activity.

1.15 Thesis Overview

The primary aim of this thesis was to understand how phase of entrainment and living against the circadian clock impacts metabolic health in T2D, with a view of guiding potential behavioural or educational interventions to improve disease management. In order to do this, a number of objectives were developed. The first objective was to determine if chronotype or SJL could independently predict glycemic control in individuals with T2D. The second objective was to investigate different conceptualisations of circadian misalignment to determine how they were related to each other and how they may impact health. The third objective was to ascertain the relationship between SJL and psychosocial stress. The final objective was to establish what influences sleep timing and causes SJL in people with T2D beyond work-imposed schedules.

Chapter 2 evaluates cross-sectionally any association between chronotype, SJL and glycemic control in a cohort of people with T2D. This chapter controls for a number of important covariates including personality factors which may also impact HbA1c levels in this cohort. **Chapter 3** goes beyond this and measures both sleep

timing variability and SJL and assesses the associations between these different indicators of circadian misalignment. This chapter also explores any association these measures have with indicators of glycemic control in healthy controls and individuals with T2D. **Chapter 4** has two parts and builds on these associations and investigates the relationship between SJL and stress. Since SJL has been associated with some negative health outcomes and is a chronic physiologic stressor, we deemed it important to investigate its association with measures of stress to determine if stress is an important mediating or moderating variable to consider. This chapter cross sectionally assesses the relationship between SJL and both general psychological stress and then work-related stress. The second part of this chapter assesses the relationship between SJL and stress reactivity in the laboratory. **Chapter 5** analyses sleep offset differences between weekdays and weekend days in a large dataset. Both the actual difference and the absolute difference are visualised, and any differences based on many demographic variables including age, sex, and socioeconomic status are explored. Associations with lifestyle variables and BMI are also investigated. Many people with T2D are retired and people who are retired and not working still display varied sleep timing and SJL. SJL during your working life is hard to suppress, and sleep timing is hard to change; however, social factors influencing this in retirement and among adults currently unemployed may be potentially modifiable. **Chapter 6** probed at what exactly is influencing sleep timing and causing either consistent sleep schedules or varied sleep timing in people with T2D who were not working. The objective here was to understand how feasible maintaining consistent sleep schedules is and to identify if those with SJL or fluctuating routines could potentially modify their behaviours. **Chapter 7** provides a general discussion of the overall results and conclusions of the research carried out in this thesis. Strengths, limitations, and areas for future research are discussed.

Chapter 2:

Cross-Sectional Evaluation of the Association between Social Jetlag and HbA1c in Adults with Type 2 Diabetes.

Parts of this chapter have been published as:

Kelly, R. M., Finn, J., Healy, U., Gallen, D., Sreenan, S., McDermott, J. H., & Coogan, A. N. (2020). Greater social jetlag associates with higher HbA1c in adults with type 2 diabetes: a cross sectional study. *Sleep Medicine, 66*, 1-9.

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Abstract

Research has suggested that later propensity to sleep and wake has been associated with poorer glycemic control in T2D. The role that SJL and personality factors play is still unclear. This study aimed to determine the relationships between chronotype, SJL and personality factors and glycemic control in T2D patients (n = 252), independently of sleep disturbances and daily caloric distribution. Patients with T2D were recruited from the annual review outpatients' clinic at Connolly Hospital, Dublin. Participants completed questionnaires, including the MCTQ and the Big Five Personality Inventory. Information on diabetes duration, current HbA1c levels, BMI was obtained from chart review. A 24-hour dietary recall was also included to estimate one day's caloric intake. Hierarchal linear regression revealed that SJL, but not chronotype or personality factors, was a significant predictor of HbA1c levels ($\beta = 0.16$, $p < .05$). Furthermore, in patients who had more than 90 minutes SJL there was a significant relationship between later chronotype and HbA1c levels ($r = 0.51$, $p = .002$), that was not observed in people with less than 90 minutes SJL. Interestingly, younger age was associated with a higher HbA1c ($r = -.23$, $p < .001$) and was partially mediated through SJL (Pm = 0.22). SJL was identified as a novel factor that was demonstrated to have a negative impact on HbA1c levels. Further study is needed to determine if this relationship could be targeted to improve glycemic control and reduce risk of secondary complications.

Keywords: Chronotype, social jetlag, personality, glycemic control, HbA1c, type 2 diabetes.

2.1 Introduction

Among the many associations between circadian rhythms and metabolic functioning, two popular areas of research involve examining the potential role of later chronotype and circadian misalignment. As discussed in chapter 1 later chronotype and SJL both have many potential negative consequences on cardiometabolic functioning. SJL has been proposed as a risk factor for several pathologies and pathophysiological conditions, including increased BMI (Parsons et al., 2015; Roenneberg et al., 2012) and T2D (Koopman et al., 2017; Wong et al., 2015). However, research in this area of diabetes management has found mixed results. Reutrakul and colleagues (2013) identified an association between later chronotype and HbA1c, but SJL was not a significant predictor. Parsons et al. (2015) reported that in a subgroup of metabolically unhealthy obese participants higher SJL and higher HbA1c levels were associated; however, when socioeconomic status and smoking was controlled for this association did not persist. Notably, recent research did not find an association between SJL or chronotype and measures of glycemia in adults with prediabetes and recently diagnosed untreated T2D (Mokhlesi et al., 2019). Research in T1D is also mixed (Larcher et al., 2016; Von Schnurbein et al., 2018).

These studies consider some important covariates but from a psychological perspective, chronotype is associated with many personality factors and its relationship with these psychological domains may help explain the impact of chronotype on (patho-) physiology (Adan et al., 2012). Evening orientation has been associated with higher extraversion and openness, while morning orientation has been associated with higher conscientiousness and agreeableness (Adan et al., 2012; Lipnevich et al., 2017). It is also possible that the association between earlier chronotype with better glycemic control could be mediated through conscientiousness as conscientiousness may be associated with better self-care and lower obesity (Skinner et al., 2014). While SJL is not dependent on chronotype individuals with a later chronotypes are more likely to have more SJL; it is therefore possible that SJL is also associated with these psychological domains. However, no clear understanding of the possible direct relationship between SJL and personality exists. Further, in young adults chronotype predicts 50% of the variation in SJL and since modern society broadly favours morning orientation, greater SJL is commonly associated with later chronotype (Roenneberg et al., 2012).

From a behavioural perspective, diabetes management is influenced by many social and psychological factors (Snoek, 2002). It is possible that the relationship between SJL, chronotype and glycemia could be understood from this perspective. For example, the amount of some food groups consumed at different points in the day has been associated with chronotype and SJL (Silva et al., 2016). SJL may have a negative impact on food behaviour as Mota et al. (2019) demonstrated an association between later mealtimes, poorer diet and SJL. Therefore, SJL may elicit behaviours that may help explain its potential role in glycemic control.

Given the mixed research to date the objective of this study was to determine firstly, if later chronotype and SJL were associated with glycemic control in patients with T2D, without any major complications. We aimed to determine if this was a direct relationship or if other sleep disturbances and psychological domains explained some of this relationship. It was hypothesised that chronotype would be associated with glycemic control, and that SJL and personality may partially mediate this association.

2.2 Methods

2.2.1 Participants

A total sample of 252 adult patients (169 males and 83 females), with T2D attending the outpatients annual review clinic at the Diabetes Centre, Connolly Hospital Blanchardstown, Dublin were recruited for this study. The estimated sample size was based on two things. Firstly, a previous study with a similar methodology recruited 190 participants (Reutrakul et al., 2013), and since this was an extension of that study with further personality variables included a slightly larger sample size was recruited. Secondly, guidelines for conducting a regression analysis were followed from the Tabernack and Fidell (2013) book and a recommended formula to calculate the minimum sample required (N> 50 + 8m, where m is the number of predictor variables). This formula recommended a minimum sample size of 138 ((50 + 8(11)). Our sample of 252 was greater than this and accounted for skew in HbA1c as the dependent variable, even after log-transformation. The study protocol was approved by the local ethics committee and conformed to the Declaration of Helsinki.

2.2.2 Clinical Variables

Chart review was used to obtain information on participants' age, weight, BMI, duration of diabetes, current medications, use of insulin and most recent HbA1c levels. Two weeks prior to the appointment all participants attended a pre-assessment clinic, and this is when HbA1c levels are assessed.

2.2.3 Self-Report Measures

The MCTQ was used to provide an estimate of participants' underlying circadian phase of entrainment and SJL (Roenneberg et al., 2003). This instrument asks about typical sleep behaviour over the previous month and has two sections. The number of work and free days was also assessed through this instrument, as was whether there was any meaningful distinction between "work" and "free" days for the participant.

The first section focuses on workdays (usually weekdays) and the second section focuses on work-free days (usually weekend days). There are six images that accompany the questions to ensure it is clear what is being asked of the participants (see appendix B). The MCTQ asks what time participants go to bed at, what time they get ready to fall asleep at, how long it takes to fall asleep, what time they wake up at,

how long it takes them to get up and if their sleep end is due to an alarm clock on both work and free days. These questions allow many variables to be calculated. Sleep onset on work and free days (SOw/SOf) can be calculated by adding the sleep latency to the sleep preparation time. Sleep end is taken as the time they report waking up at. By subtracting the sleep onset from the sleep end, you can get the typical sleep duration on work and free days.

$$SDw = SEw - SOw$$
$$SDf = SEf - SOf$$

Midsleep on work and free days (the midpoint between sleep onset and wake time), can be calculated by adding half the sleep duration to the sleep onset time.

$$MSW = SOw + (SDw/2)$$
$$MSF = SOf + (SDf/2)$$

Average sleep duration over the course of a week was calculated using a formula that weighted the amount of self-reported sleep on "work" and "free" days (Roenneberg et al., 2012). Sleep duration on workdays was multiplied by the number of workdays and added to sleep duration on free days multiplied by the number of free days; this value was then divided by 7 to get an average daily sleep duration.

$$SDweek = [(SDw \times WD + SDf \times FD)/7]$$

MSF corrected for sleep debt accumulated during the week, provides a measure of chronotype. This estimates phase of entrainment, when there are no social obligations influencing sleep and stops sleep debt having an impact (Roenneberg et al., 2003). If the individual oversleeps at the weekend and sleep debt is present the difference between sleep duration on a free day and the average weekly sleep duration is calculated and divided by two and then subtracted from the original MSF.

$$\text{If } SDf > SDw: MSFsc = MSF - ((SDf - SDweek)/2)$$

$$\text{If } SDf \leqslant SDw: MSFsc = MSF$$

Absolute SJL is calculated by subtracting mid-sleep on workdays from mid-sleep on free days and getting the absolute difference (Wittmann et al., 2006)

$$\text{Absolute SJL} = |\text{MSF} - \text{MSW}|$$

The Centre for Epidemiologic Studies Depression (CES-D) Scale. Depressive symptomatology and mood were assessed via the CES-D scale (Randolf, 1977). The CES-D is a well validated scale for assessing depressive symptomatology and was also utilised in the study conducted by Reutrakul and colleagues (2013). Consistency in measures between our study and the study by Reutrakul et al. (2013) allows closer comparison of the findings. Participants were required to rate several statements regarding their mood over the previous week from rarely/none of the time (less than one day) to most/all of the time (5-7 days). Questions included for example "I was bothered by things that usually don't bother me." and "I enjoyed life". Each question was scored between 0 and 3 and positively worded questions were reverse scored. Higher scores indicate more depressive symptoms, the possible range is 0-60 and 16+ indicates risk of clinical depression (Randolf, 1977).

The Big Five Personality Inventory. The 44 item Big Five Personality Index is a multidimensional personality inventory, and it begins with the statement "I see myself as someone who ...", followed by 44 short phrases that an individual rates on a five-point Likert scale, where 1 corresponds to "disagree strongly" to 5 corresponding to "agree strongly". This scale was used to assess the five major personality domains: extraversion, agreeableness, conscientiousness, neuroticism, and openness (John & Srivastava, 1999). The Big 5 is a common framework for assessing personality and this scale was utilised as it is an efficient and widely used measure of personality (John & Srivastava, 1999; John et al., 2008). Questions include for example "I see myself as someone who ... is talkative". Each personality domain is measured with a specific number of questions which dictates its range in scores, extraversion and neuroticism have eight questions meaning scores can range from 8 - 40, agreeableness and conscientiousness have nine questions meaning scores can range from 9 – 45 and openness has ten questions meaning scores can range from 10 – 50. Higher scores on each scale indicate that the individual had higher levels of that trait.

The Pittsburgh Sleep Quality Index (PSQI). The PSQI was used to evaluate subjective sleep quality over the previous month. The PSQI is composed of seven components around subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction (see Appendix C). Each of these are scored from 0-3 and then totalled with a possible range of 0-21. As the global score increases sleep quality decreases and a global score greater that 5 is classed as poor sleep quality (Buysse et al., 1989).

The Berlin Questionnaire. The Berlin Questionnaire was used to assess the risk of obstructive sleep apnea (OSA) in participants without a previous diagnosis. The Berlin scale is a simple instrument with 3 categories. Each section is scored as either positive or negative, if 2 or more are positive the individual is classed as high risk while if one or none is classed as positive the individual is classed as low risk (Netzer et al., 1999). Participants in this study were categorised as low risk, high risk, or having an existing OSA diagnosis.

2.2.4 Dietary Recall

The participants all filled in a dietary recall. This asked for information on all main meals and snacks consumed over the previous 24 hours. A similar technique has been used in previous studies including Reutrakul et al. (2013). Participants were asked to rate portion sizes as small/medium or large and provide brand names and all minor details where possible. Caloric content was calculated using online databases (www.myfitnesspal.ie; www.nutracheck.co.uk) and restaurant and manufacturer websites. Total daily calories and calories in meals classed as breakfast, lunch, dinner, or snacks were calculated. Where specific examples and brands were detailed the restaurant and manufacturer websites provide accurate information while the databases have accurate caloric information for different portions of all generic foods. Information on caffeine intake was not estimated as part of this.

2.2.5 Procedure

T2D patients attending their scheduled outpatient's appointment at the clinic were approached on arrival to the waiting room. This clinic ran from 08:30-12:30 every week. Patients interested in the study were initially screened to see if they met the inclusion and exclusion criteria and given a detailed information leaflet. Around 100 participants were recruited between 2014 and 2015, and the remaining 152

partcipants were recruited between 2016 and 2017. To be eligible for the study patients needed to be aged 18 years or above, have a diagnosis of T2D in the absence of serious diabetes complications and medical co-morbidities and be able to provide informed consent. Absence of serious complications was primarily based on the participants attending the annual review clinic. This clinic involved straightforward cases of T2D, that did not need any specialist attention outside of the routine yearly check-up. Night shift-workers were excluded due to the significant circadian disturbance experienced. Informed consent was obtained from all participants. After informed consent was obtained the participants were then provided with a questionnaire booklet and the 24-hour dietary recall form. Participants had a choice to either fill out the surveys by themselves under the supervision of the researcher or the researcher assisted them with the questionnaires. Medical files were reviewed by doctors and nurses to obtain clinical values when the clinic had finished for the day.

2.2.6 Data Analysis

Decimalised time was used throughout. For example, when analysing all circadian variables (i.e., MSFsc, SJL) 7:30 became 7.5, 45 minutes became .75. Data was assessed for potential violations of the assumptions of the general linear model. When assessing normality, histograms and plots were used to visually inspected the data and skewness and kurtosis values greater than +/- 2 were taken to indicate a substantial deviation from normality. Some variables violating the assumption of normality were common log transformed which reduced skewness and kurtosis and improved the overall distribution. Log 10 HbA1c was used throughout in correlation and regression analysis. If following transformation that a variable was still displaying a large deviation from the normal distribution, the correct non-parametric analysis was conducted, and results were reported as median and interquartile range (IQR). Correlation analysis was used to assess the relationship between glycemic control and demographic, personality, circadian and dietary variables, Pearson product moment correlation and Spearman's rank order correlation were both utilised. To assess any independent association between chronotype and HbA1c beyond demographic, and mood variables already known to influence HbA1c a hierarchal linear regression was conducted. This model also controlled for personality and sleep variables identified through previous univariate analysis (those with $p < .1$ for their association with HbA1c), whilst ensuring that the assumptions of multicollinearity, normality of

distribution of residuals and homoscedasticity were not violated. The PROCESS macro for SPSS developed by Hayes (2017) was used to conduct a moderation and mediation analysis. Bootstrapping was used with 1,000 samples for both sets of analysis. With the PROCESS tool model 1 was used to conduct simple moderation and model 4 was used to conduct simple mediation. All statistical analysis was conducted using IBM SPSS (V25, IBM Corporation) or JASP (V 0.9.1.0, https://jasp-stats.org/).

2.3 Results

Demographic and clinical details of all 252 participants are detailed in Table 2.1. The mean age of participants recruited was 61.9 years (*SD* = 10.5, range 31 to 87). Regarding BMI, 62.2% of patients were obese, of these 25.5% had severe obesity. 32.7% of participants were overweight and 5.2% were normal weight according to standard BMI guidelines where 18.5-24.9 kg/m^2 was classed as normal weight, 25-29.9kg/m^2 was overweight, 30-34.9kg/m^2 was obese and >35kg/m^2 was severe obesity. Median years with diabetes was 7 and median HbA1c level was 6.9% (52 mmol/mol). 16.3% of patients were currently being treated with insulin.

Analysis of circadian variables showed that the average midsleep on free days corrected for oversleep was 3:53 am while median SJL was 15 minutes. A large range in SJL values was observed (0 to 304 minutes). Just over half of the sample (51%) reported good subjective sleep quality (reflected by a global PSQI score of 5 or less). Just over half of the population scored as high risk for OSA (50.4%) and a diagnosis was present in 2.4%. OSA was analysed as a dichotomous variable with high risk and diagnosis grouped together due the small number of people with an OSA diagnosis.

Table 2.1

Demographic, clinical, sleep and personality descriptives for the study sample.

	n = 252
Clinical Parameters	
Age (years)	61.85 +/- 10.54
Male (n %)	169 (67.1)
BMI (kg/m^2)	32.12 +/- 5.37 n = 251
Normal weight	13 (5.2%)
Overweight	82 (32.7%)
Obesity class I	92 (36.7%)
Obesity class II	64 (25.5%)
Duration of diabetes (years)	7 (4-11.5) n = 232
</= 5	79 (34.1)
6-10	90 (38.8)
11-20	56 (24.1)
> 20	7 (3.0)
Insulin use (n, %)	41 (16.3%) n = 251
HbA1c (mmol/mol)	52 (46-62)
HbA1c (%)	6.9 (6.4-7.8)
CES-D Score	10.01 (9.31) n = 240
Circadian Parameters	
Corrected Midsleep (MSFsc) (h)	3.88 (1.26)
Absolute Social Jetlag (decimalised mins)	0.25 (0.00-0.95)
Sleep Parameters	
Average sleep duration	7.62 (6.95-8.5)
Global sleep quality	5.99 (3.66) n = 249
PSQI score > 5	122 (49%)
Sleep onset workdays	23.70 (1.50)
Sleep end workdays	7.33 (1.46)
Sleep onset free days	00.09 (1.48)
Sleep end free days	8.02 (1.66)
Sleep apnea risk (n %)	132 (52.8) n = 250
Personality data	n = 244
Extraversion	25.33 (6.52)
Agreeableness	36.33 (5.74)
Conscientiousness	35.45 (6.80)
Neuroticism	21.63 (6.98)
Openness	32.28 (7.98)
Dietary Parameters	n = 157
Total daily calories	1321 (370)
Breakfast calories	332 (147)
Lunch calories	319 (187)
Dinner Calories	472 (188)

Note. Data are means ± SD (for normally distributed variables), median (25th percentile – 75th percentile; for variables violating the assumption of normality) or n (%; number of cases and the percentage that this is for categorical variables). BMI; Body Mass Index, CES-D; Centre for Epidemiologic Studies Depression scale, PSQI; Pittsburgh sleep quality index, OSA; Obstructive sleep apnea.

2.3.1 Initial Correlation Analysis

Correlation analysis of common log transformed HbA1c with demographic, dietary, personality and circadian and sleep variables are displayed in Table 2.2. Higher HbA1c levels were associated with higher CES-D an indicator of more depressive symptoms (r = .22, p = .001), longer disease duration (*rho* = .17, p = .01), higher BMI (r = .18, p = .005) and younger age (r = -.23, p < .0005). HbA1c levels were not associated with any measures of caloric intake. No significant correlations were observed with total daily caloric intake, breakfast caloric intake, lunch caloric intake or dinner caloric intake (see Table 2.2). Regarding personality, higher HbA1c was associated with lower conscientiousness (r = -.13, p = .041) and higher neuroticism (r = .19, p = .003) and no significant correlations were observed with extraversion, openness, or agreeableness. Sleep quality and average sleep duration were not significantly correlated with HbA1c levels. Furthermore, MSFsc and HbA1c were not significantly correlated, although SJL was significantly and positively correlated with HbA1c (*rho* = 0.23, p < .001).

Table 2.2

Correlation analysis of log HbA1c with clinical factors, personality factors and sleep variables.

	r	p-value
Clinical Parameters		
Age	-.23***	.0003
BMI	.18**	.005
CES-D	.22**	.001
Diabetes Duration[a]	.17*	.01
Dietary Parameters		
Total Daily Calories	.02	.86
Breakfast Calories	-.06	.46
Lunch Calories	-.02	.78
Dinner Calories	-.07	.42
Personality Data		
Neuroticism	.19**	.003
Conscientiousness	-.13*	.04
Openness	.03	.67
Agreeableness	-.03	.62
Extraversion	-.03	.67
Sleep Parameters		
MSFsc	.11	.09
SJL[a]	.23***	.0003
Sleep Quality (PSQI)	.03	.61
Sleep Onset WD	.05	.39
Sleep End WD	-.06	.33
Sleep Onset FD	.12	.06
Sleep End FD	.14*	.03
Average sleep duration[a]	-.08	.23

Note. Superscript [a] indicates violation of normality and Spearman's rho correlation, all other correlations Pearson's r.

2.3.2 Linear Regression Analysis

A hierarchical multiple regression analysis was undertaken with Log10HbA1c as the dependent variable. All demographic and clinical variables known to influence HbA1c were entered in the first block (sex, age, BMI, Berlin score, duration of diabetes, insulin use and CES-D scores; model 1), personality variables that showed a relationship with HbA1c in previous correlation analysis were entered in block 2

(neuroticism and conscientiousness; model 2), sleep and circadian variables that showed a significant relationship (SJL) and had previously been shown to play a role (MSFsc) were entered in the final block (SJL, MSFsc; model 3; Table 2.3). The predictor variables entered were either those known to influence HbA1c or those that showed a $p < .10$ in the preceding correlation analyses. Prior to conducting the analysis, the assumptions of a regression model were assessed. Particular attention was paid to the association between SJL and MSFsc in order to ensure there were no multicollinearity as these variables often show a moderate association. A weak correlation was observed (*rho* = .267, $p < .0005$; Figure 2.1). The first block which included demographic variables explained 23.2% of the variance in HbA1c. Age, duration of diabetes and insulin use were the significant predictors in this model. Block 2 which included the personality variables, neuroticism and conscientiousness did not significantly change R^2. Addition of block 3, SJL and MSFsc increased the variance in HbA1c explained to 25.7% ($R^2 = 0.257$), with age, insulin use and SJL being a significant predictors.

Table 2.3

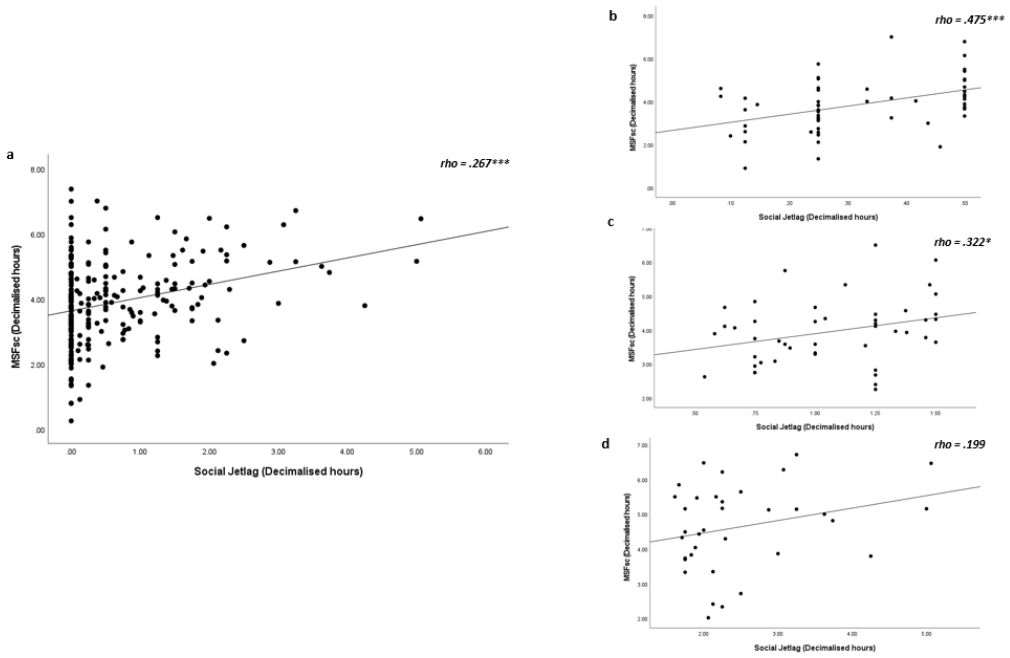
Relative contribution of each variable toward the variance in log of HbA1c.

	Model 1		**Model 2**		**Model 3**	
	R^2=0.23***		**R^2=0.23**		**R^2=0.26***	
Variable	β	95% CI	β	95% CI	β	95% CI
(1) Sex	-.02	-.14;.10	-.02	-.15; .10	-.02	-.15; .10
(1) Age	-.23**	-.36;-.10	-.23**	-.36;-.10	-.17*	-.31; -.03
(1) BMI	.05	-.08;.18	.04	-.09; .17	.04	-.09; .17
(1) Berlin	.04	-.09;.17	.04	-.09; .17	.01	-.12; .15
(1) Diabetes duration	.14*	.00;.27	.14*	.00; .28	.13	-.00; .27
(1) Insulin use	-.31***	-.44;-.18	-.31***	-.44;-.18	-.32***	-.45;-.20
(1) CES-D	.12	-.00;.25	.10	-.06; .25	.12	-.03;.28
(2) Conscientiousness			-.03	-.17;.10	.00	-.14; .14
(2) Neuroticism			.03	-.13; .18	.02	-.13; .18
(3) SJL					.16*	.02; .29
(3) MSFsc					.04	-.10;.17

Note. Relative contribution of each variable toward the variance in log of HbA1c including Standardised Beta value 95% confidence interval (CI) for each variable. Analyses were conducted with a hierarchical multiple regression model and all variables with a p-value < .10 when correlated with log HbA1c in the bivariate analysis were included. Model number at which entered is indicated for each predictor in parentheses.

Figure 2.1

The association between MSFsc and SJL.



Note. **Figure a.** shows the overall association, **figure b.** shows the association in the group with less than 30 minutes SJL, **figure c.** shows the association in those with 30-90 minutes SJL, and **figure d.** shows the association in those with greater than 90 minutes of SJL.

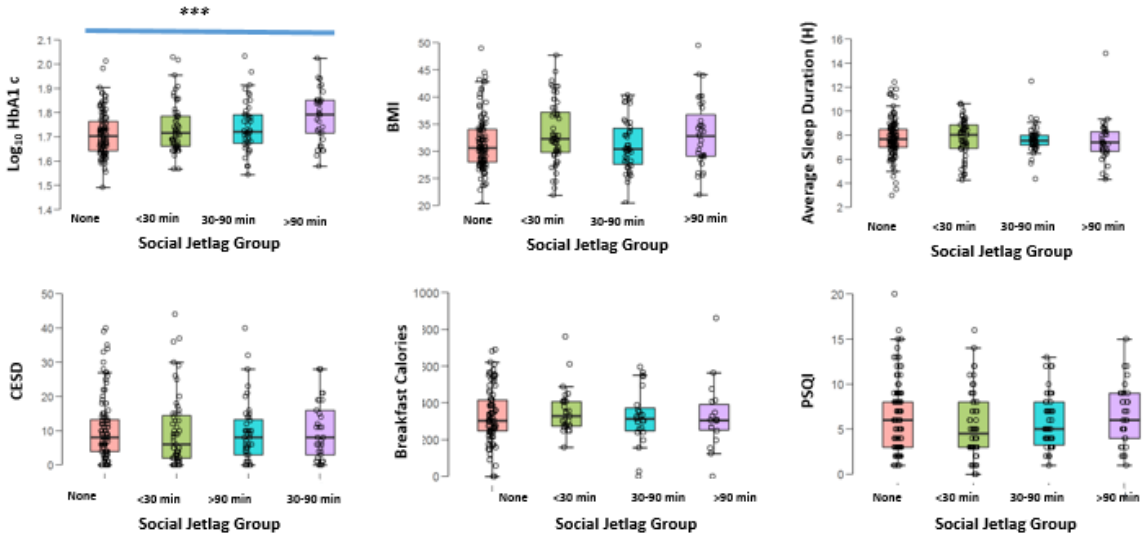
2.3.3 Groupwise Analysis

Due to the association between SJL and HbA1c, SJL was broken into four groups and analysed as a categorical variable. The four SJL groups were those with zero SJL (N = 114), those with low SJL (less than 30 minutes; N = 57), those with moderate SJL (between 30 and 90 minutes; N = 46) and those with high SJL (more than 90 minutes; N = 35). This allowed to test for any dose-response relationships between SJL and HbA1c. HbA1c levels differed significantly between these four SJL groups ($F_{3,248}$=5.7, p < .001), with Tukey *post-hoc* analysis demonstrating that the group with SJL of > 90 minutes had higher HbA1c levels than those with no SJL (p < .001, Cohen's d = -.815; Figure 2.2). An ANCOVA was conducted with MSFsc as a covariate and this effect remained ($F_{3, 247}$ = 4.83, p = .003). Differences in demographic

and clinical variables between groups were then assessed. There was no difference in BMI (p = .056), average sleep duration (p = .383), CES-D score (p = .973), breakfast calories (p = .848) or total PSQI score (p = .394; Figure 2.2) between SJL groups. Since BMI displayed a p value below .1 the relationship between SJL and BMI was analysed. BMI and SJL were not correlated overall (*rho* = .074, p = .245) or in any of the SJL groups (Figure 2.3). Furthermore, personality variables did not vary significantly between SJL groups (Table 2.4). Age differed significantly across SJL groups, the high SJL group was significantly younger when compared to the no and low SJL groups (p < .001; Table 2.4). The duration of diabetes also differed between groups (p = .044); but no differences were observed between groups when post-hoc comparisons were conducted.

Figure 2.2

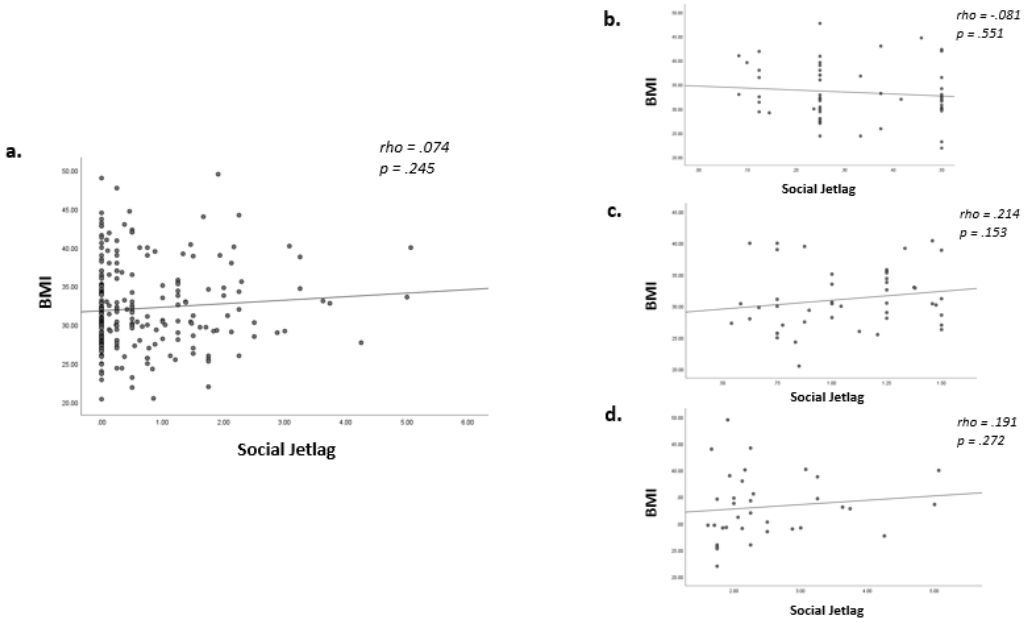
Boxplots illustrating scores for log HbA1c, BMI, sleep duration, CESD, calories consumed at breakfast and PSQI in groups with no SJL, SJL of less than 30 minutes, SJL of between 30 and 90 minutes and SJL of greater than 90 minutes.



Note. Statistical analysis with one way ANOVA, (p < .001 for HbA1c, p = .056 for BMI; p = .383 for sleep duration, p = .973 for CES-D; p = .848 for breakfast calories; and p = .394 for PSQI). *** denotes p < .001 pairwise post-hoc comparisons. n = 252, except for BMI (n = 251), CESD (n = 240), breakfast calories (n = 157), and PSQI (n = 249).

Figure 2.3

The association between SJL and BMI.



Note. **Figure a.** shows the overall association between SJL and BMI; figure **b.** presents the correlation between SJL and BMI in the group with less than 30 minutes of SJL, figure **c**. demonstrates this association in the group with 30-90 minutes of SJL and figure **d.** demonstrates this association in the group with greater than 90 minutes SJL. The association is not statistically significant in any group.

Table 2.4

Demographic, clinical, sleep, circadian, personality and dietary variables across the four social jetlag groups.

	No SJL (n = 114) A	SJL < 30 minutes (n = 57) B	30-90 mins SJL (n = 46) C	> 90 mins SJL (n = 35) D	p-value
Demographic & Clinical Parameters					
Age (years)	66.28 (9.32)[CD]	62.65 (8.84)[CD]	55.93 (9.96) [AB]	53.85 (9.55) [AB]	<.001
Male (n, % within group)	78 (68.4)	40 (70.2)	29 (63.0)	22 (62.9)	.810
BMI (kg/m²)	31.54 (5.01) (N = 97)	33.43 (5.78) *(N=56) (N = 55)	31.14 (4.84) (N = 45)	33.12 (6.11) (N = 35)	.056
Duration of diabetes (years)	8 (4.5-13)	8 (5-13)	7 (4-10.5)	6 (3-9)	.044
Insulin dependent (n, % within group)	17.5 (20)	17.5 (10)	15.6 (7) *(N=45)	11.4 (4)	.845
HbA1c (mmol/mol)	50.50 (44-58)[D] (N = 108)	52.00 (46-61) (N = 55)	52.50 (47-62) (N = 44)	62 (52-71) [A] (N = 33)	.002
CES-D Score	10.24 (9.14)	9.90 (10.45)	9.48 (8.90)	10.18 (8.73)	.973
Sleep & Circadian parameters					
Average sleep duration	7.67 (7.00-8.56)	8.04 (6.92 – 8.87)	7.56 (7.17 – 8.02)	7.39 (6.67-8.31)	.383
MSFsc	3.63 (1.33) [D]	3.87 (1.22) [D]	3.96 (0.95)	4.63 (1.23) [AB]	.001
Sleep onset workdays	23.74 (1.61)	23.87(1.20)	23.49(1.19)	23.60(1.90)	.602
Sleep end workdays	7.52 (1.49) [D]	7.67 (1.60) [D]	7.00 (0.99)	6.62 (1.38) [AB]	.001
Sleep onset free days	23.73 (1.60)[D]	00.12(1.29)[D]	00.26(1.15)	00.99(1.38)[AB]	<.001
Sleep end free days	7.52 (1.49) [CD] (N = 114)	7.76 (1.58) [D] (N = 56)	8.36(1.35) [AC] (N = 46)	9.64(1.61) [ABC] (N = 33)	<.001
PSQI	6.18 (3.86) (N = 113)	5.29 (3.75) (N = 56)	6.00 (3.21) (N = 46)	6.48 (3.36) (N = 35)	.394

OSA Risk (n, % within group)	56 (49.6)	28 (50.0)	23(50.0)	25(71.4)	.129
Personality Factors					
	(N = 110)	(N = 55)	(N = 46)	(N = 33)	
Extraversion	26.27 (6.39)	24.18 (6.50)	23.83 (6.13)	26.21 (7.06)	.069
Agreeableness	36.57 (6.04)	36.42(5.26)	35.70 (6.44)	36.24 (4.5)	.856
Conscientiousness	36.34 (6.26)	35.44 (6.92)	35.24 (7.14)	32.82 (7.45)	.076
Neuroticism	20.70 (6.62)	21.93 (7.73)	22.63 (6.79)	22.82 (7.01)	.268
Openness	33.31 (7.88)	31.85 (8.24)	31.11 (7.45)	31.18 (8.46)	.309
Dietary Parameters					
	(N = 89)	(N = 27)	(N = 23)	(N = 18)	
Total daily calories	1297 (361)	1360 (284)	1410 (470)	1273 (395)	.516
Breakfast calories	329 (146)	355 (123)	322 (155)	326 (186)	.848
Lunch Calories	308 (178)	321 (178)	397 (243)	270 (150)	.140
Dinner Calories	471 (168)	455 (191)	493 (224)	476 (234)	.913

Note. Table showing the means (SD), median (IQR) or n (% within SJL group) of variables across the four social jetlag groups. A refers to the no SJL group, B refers to the group with less than 30 minutes SJL, C refers to the group with 30-90 minutes SJL and D refers to those with > 90 minutes SJL. One way ANOVA analyses was conducted in the normally distributed continuous variables, Kruskal Wallis test was conducted where the assumption of normality was violated (diabetes duration, HbA1c mmol/mol, average sleep duration). Chi square test for independence was utilised in the case of a categorical variable to determine any associations between variables. Significant differences between groups is noted with superscript annotations (^{A},^{B},^{C},^{D} depending on which group it differs from). Missing data is noted within, either in superscript where only one group had missing data or in the row above where more than one group had missing data.

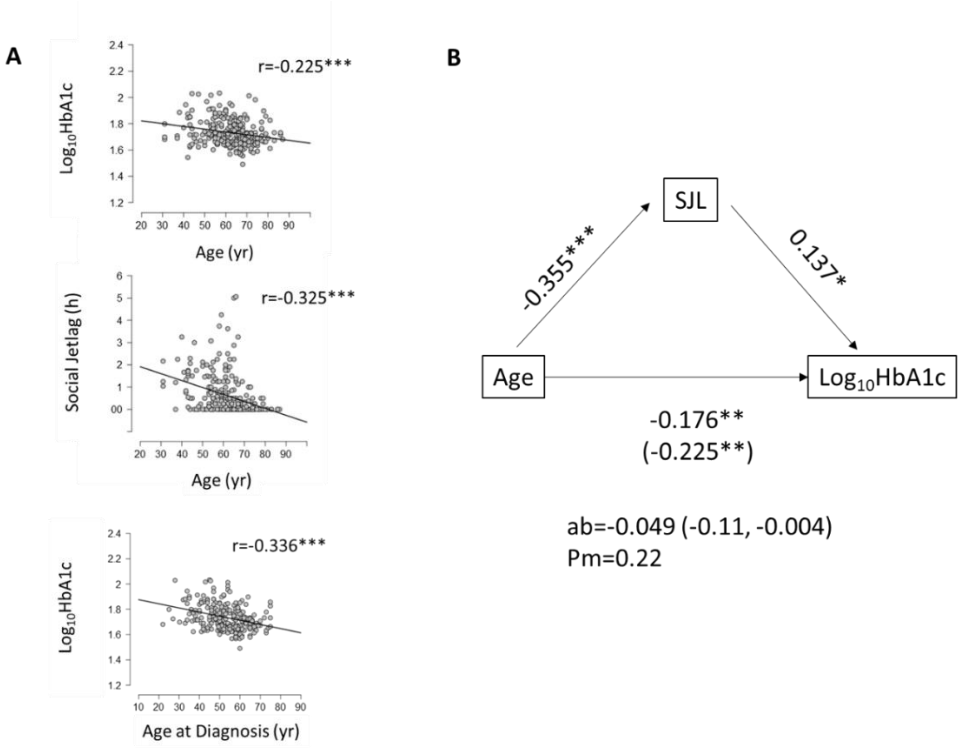
2.3.4 Mediation Analysis SJL, Age and HbA1c

An ANCOVA was run on HbA1c levels and SJL group, with age and diabetes duration as covariates to control for their potential confounding effect. The effect of SJL on HbA1c persisted when controlling for age and diabetes duration (p = .022) with the high SJL group having a significantly higher HbA1c than the no SJL group (p = .012, Cohen's d = -.653). Notably, younger age and higher HbA1c were associated in the study sample (r = -.225, p < .001). This was somewhat unexpected and as younger age is also associated with SJL in our sample, a mediation analysis

was conducted of the association between younger age with higher HbA1c levels. This analysis demonstrated that this relationship is partially mediated through SJL (22% of the association between younger age and HbA1c levels was mediated through SJL; Figure 2.4).

Figure 2.4

Relationship between SJL, age and HbA1c.



Note. **(A)** Scatter plots illustrating the relationships between age and age at diagnosis with log HbA1c and SJL. *** p < .001. **(B)** Mediation of the relationship of age and log HbA1c via SJL, which accounts for 22% of the relationship (Pm: percentage mediation). Ab = indirect effect, with 95% confidence interval in parentheses.

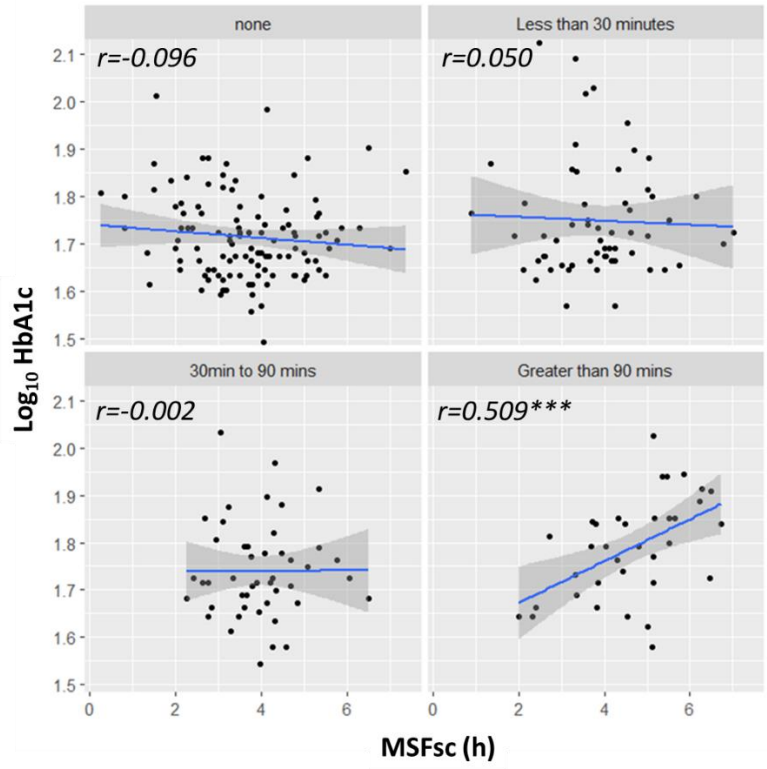
2.3.5 Moderation Analysis HbA1c and MSFsc

Further analysis was conducted to explore the lack of the previously described relationship between HbA1c and MSFsc in our data. A moderation analysis of the relationship between MSFsc and HbA1c, with SJL group as the moderator was conducted and it was found that including the MSFsc x SJL group term increased R^2 by 0.043, and that this interaction was significant (p = .001). Essentially, MSFsc was

associated with HbA1c levels, but only in the presence of high levels of SJL (r = .51, p = .002 between MSFsc and HbA1c in participants with more than 90 minutes SJL; Figure 2.5). In the no, low, and moderate SJL groups no association between MSFsc and HbA1c levels was observed. MSFsc range in the four SJL groups was similar (Figure 2.6). The data also suggests that the relationship between HbA1c and MSFsc in this group is not simply due to those participants with later MSFsc also significantly having more SJL. As in the SJL > 90mins group, no significant association between SJL and HbA1c (r = -.232, p = .179), or between SJL and MSFsc (r = .266, p = .123) was observed.

Figure 2.5

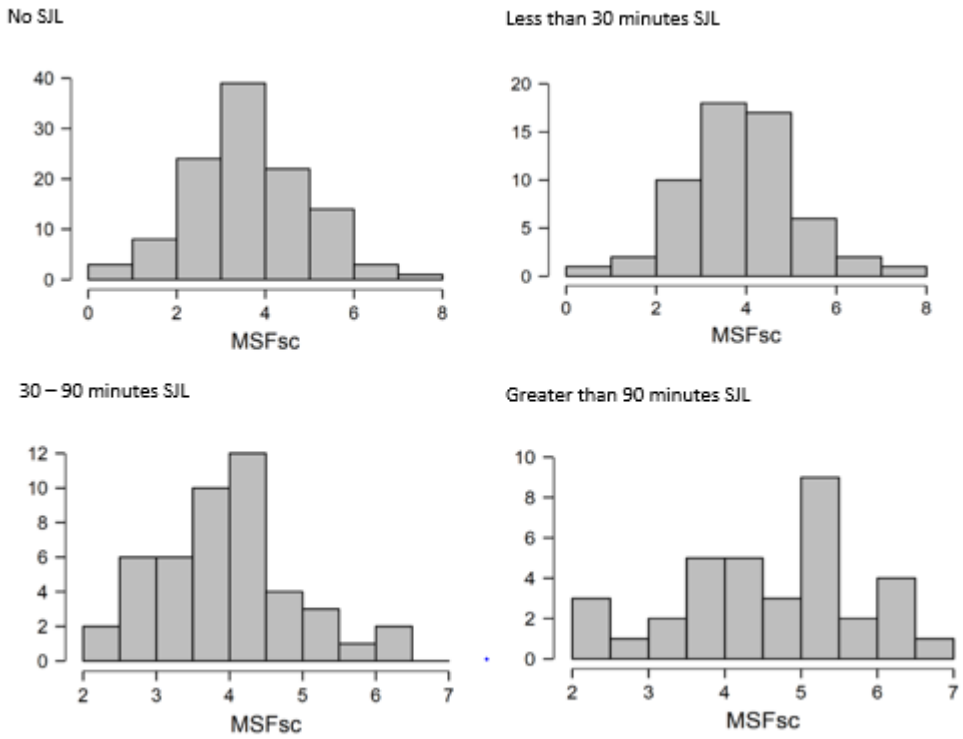
Relationships between log HbA1c and MSFsc for participants with zero, minimal, moderate, and large SJL.



Note. The shaded area represents the 95% confidence interval of the regression line. Analyses by Pearson correlation. (Zero, n = 114, less than 30 minutes, n = 57, 30-90 minutes, n = 46, greater than 90 minutes, n = 35).

Figure 2.6

Distributions of MSFsc across the four SJL groups.



Note. Figure shows that the range of SJL is broadly similar in each of the four groups.

2.4 Discussion

This current study set out to examine the association between chronotype, SJL, personality and glycemic control in a cohort of people with T2D. The main finding from this study is that recurring circadian misalignment from workdays to free days, typified by SJL predicted poorer glycemic control. Chronotype and personality were not significant predictors in this model. Interestingly, among a subgroup of participants with more than 90 minutes of SJL, later MSFsc and higher HbA1c was associated. This suggests a novel interaction between SJL, MSFsc and HbA1c. It is likely that the majority of SJL reported in this study of older adults is due to social factors and that SJL and MSFsc are mostly non-colinear. The correlation between SJL and MSFsc in this study is much weaker than normally observed in younger participants (Roenneberg et al., 2012). This interaction between SJL and MSFsc is therefore probably due to an interplay of social and circadian characteristics. These results suggest a role of circadian misalignment, in glycemic control in T2D. This is not exactly in line with previous research regarding the independent association between later chronotype, not SJL and poorer glycemic control in T2D and prediabetes (Anothaisintawee et al., 2017; Reutrakul et al., 2013). Identifying the nature of the social factors that shape SJL may provide novel psychosocial and psychoeducational targets to improve self-care in T2D.

While most participants in this sample were overweight or obese, those with high SJL did not have higher BMI than patients with no SJL, and BMI was controlled for in the regression analysis. This is in line with previous research as Reutrakul et al. (2013) also reported an association between chronotype and HbA1c in a T2D sample independent of BMI. No association between personality variables and HbA1c was observed in our regression model which suggests that the association between SJL, chronotype and HbA1c cannot be explained by personality. Glycemic control was found to be associated with insulin use and mood; however, these did not differ between SJL groups. The relationship between age, SJL and HbA1c that was observed was interesting but unexpected. Higher HbA1c in younger adults suggested that they may have more severe disease, which has been reported recently (Shamshirgaran et al., 2017). Individuals with the greatest SJL were younger than individuals with no SJL in our study, which is possibly expected as younger age is generally associated with later chronotype and the social imperatives here may result in more SJL.

However, this relationship remained the same when years since diagnosis and age were controlled for and a mediation analysis revealed that SJL explains around 20% of the effect of age on HbA1c. This suggests that SJL may be a more important target for particular age groups with T2D. This is in line with previous research carried out by Koopman et al. (2017) who found an association between SJL and diabetes prevalence only in individuals 61 years and younger.

A potentially important factor that may help explain some of the relationship between SJL and glycemic control especially in younger working age populations is work-related stress. Our population included some older participants who are retired and their SJL may be lower or diminished due to the lack of work demands and some younger and still employed. Greater stress in the workplace may impact disease severity (Kawakami et al., 2000). However, one study did report that HbA1c in T2D participants was not impacted by workplace psychosocial stress (Annor et al., 2015). The relationship between stress and SJL needs to be unravelled to fully understand this potential relationship.

How T2D disease severity is influenced by chronotype and SJL is not currently clear. The relationship between metabolism and the circadian clock is complicated and most likely bidirectional, in that metabolic input modulates clock-dependent gene expression and the circadian clock profoundly effects metabolic functioning (Panda, 2016). Later chronotype may lead to more internal desynchrony between peripheral clocks which may in turn cause systemic pressures resulting in poorer response to medication in diabetes or simply poorer glycemic control (Roenneberg & Merrow, 2016). Circadian misalignment can directly be linked with blood glucose control due to inadequate pancreatic β-cell function; it can cause reduced glucose tolerance and insulin sensitivity (Morris, Yang et al., 2015; Scheer et al., 2009). Scheer et al. (2009) demonstrated pre-diabetic states of postprandial glucose responses in healthy participants after eight days of forced circadian misalignment and Leproult et al. (2014) has demonstrated metabolic disruption due to increased inflammation in people with mistimed daytime sleep. Previous research has also suggested an association between circadian disruption and elevated fasting plasma glucose, elevated free fatty acid levels and lower insulin-simulated glucose disposal (Wefers et al., 2018). Circadian misalignment has been implicated in the alteration of many plasma proteins

that are important for metabolic regulation (Cedernaes et al., 2015; Depner et al., 2018). SJL may be acting in a similar manner as circadian disruption is in these studies.

SJL is often associated with wakefulness during the individual's biological night due to work and social commitments. In this scenario melatonin levels may still be raised in the chronological morning (Wright et al., 2013) and insulin sensitivity and glycemic control could be influenced. In our study HbA1c and average sleep duration showed no relationship suggesting that circadian misalignment independently influences HbA1c.

This study has some notable strengths in that it involved a well-defined clinically representative sample, and it replicated a previously published approach with minor modifications (Reutrakul et al., 2013). However, in interpreting the findings of this current study there are important caveats and weaknesses to consider. Firstly, all relationships observed are associations and cannot be described as causal due to the cross-sectional and observational nature of the study. While a mechanism for this directional impact is unknown it is possible that glycemic control influences SJL and not the other way around. Potentially through physiological sleep system changes due to altered glycemia. Secondly, these were all self-report measures, and while well validated, participants motivation and memory are key factors here. Objective measures would provide more detail on the complexity of sleep-activity behaviour in this cohort. This is also true for the dietary recall; socially desirable responding of more acceptable food choices may have been reported. It is possible that people rate portion sizes differently and this would also influence the estimation of calories consumed. In future more detail is needed on recall on different days during the week. It would be interesting to note if food behaviours on work and free days differ substantially and if this may play a role in glycemic control. In addition, details on the precise timing of food is key and longer food logs with timestamps will allow this. Thirdly, the subgroup of people with highest SJL was smaller and this should be remembered when interpreting the relationship between chronotype and HbA1c here. Finally, more details on work schedules, including early/late hours and stress need to be captured, we did not measure information on the participants work schedules beyond the number of free and workdays per week. Further analysis of lifestyle factors including physical activity, medication compliance and weight stability are required as these could all vary with SJL experienced.

In conclusion, the results of this study suggest a role for circadian misalignment in diabetes disease management. In patients with T2D, an independent association between greater SJL and higher HbA1c was observed. Furthermore, in individuals with the highest SJL ($\geq$ 90 minutes) a strong association between a later chronotype and poorer glycemic control was observed. This indicates a novel interaction between SJL, chronotype and glycemic control. Of further interest, this study suggests that younger patients may be more susceptible to greater SJL, and this may have an impact on their glycemic control. Participants with the most SJL were the youngest and the youngest also had higher HbA1c on average. Circadian factors may play a more important role in regulating metabolism in younger than in older adults with T2D. Research to fully understand SJL in working aged individuals and if it related to workplace psychosocial stress is crucial here to determine if this relationship between circadian misalignment and measures of glycemia is direct or if other lifestyle variables or stress levels are playing a role. Research on what is causing SJL among older individuals who might not be working is also crucial in order to see what the driving factors are outside of the workplace and if these could be reduced or eliminated. More research could lead to cost-effective, non-pharmacological interventional studies to reduce SJL.

The next chapter goes beyond the self-reported measure of SJL utilised here in chapter 2. Actigraphy is used to provide an objective measure of SJL and additional measures of sleep timing variability. This will provide a more in-depth picture of circadian misalignment in a sample of participants with T2D and healthy controls. Furthermore, their association with HbA1c and additional indicators of blood glucose control will be explored.

Chapter 3:

Sleep Timing Variability, SJL, Interdaily Stability and Intradaily Variability in a cohort of Healthy Middle-Aged Adults and those with T2D.

Parts of this chapter have been published as:

Kelly, R. M., Healy, U., Sreenan, S., McDermott, J. H., & Coogan, A. N. (2022). An Exploratory study of the association of sleep timing variability with cardiometabolic health in healthy middle-aged adults and those with type 2 diabetes. *Chronobiology International, 39*(4), 569-578.

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Abstract

Sleep is increasingly recognised as an important risk factor for metabolic disease and an important factor for severity of established metabolic disease. Apart from well-studied sleep parameters such as average sleep duration and subjective sleep quality, focus has recently been brought to examining whether sleep timing variability (the day-to-day fluctuations of sleep timing) may be important factors in metabolic diseases such as T2D. In the current study we have explored the associations of measures of sleep timing variability, SJL and circadian rhythm parameters, namely interdaily stability and intradaily variability as determined from actigraphy. In addition, we investigated any associations these measures had with cardiometabolic measures in a group of healthy control middle-aged adults (N = 27) and adults with well-controlled uncomplicated T2D (N = 30). We found no groupwise differences in various measures of sleep timing variability apart from self-reported SJL (which was greater in the diabetes group). In the diabetes groups, HbA1c levels were inversely correlated with variability in sleep onset (*rho* = -.481, p = .010), midsleep (*rho* = -.416, p = .027) and sleep duration (*rho* = -.398, p = .036), although HOMA-IR did not correlate with any of these measures. In the diabetes group there were no associations between sleep timing variability measures and metabolic biomarkers (cholesterol, LDL, HDL, triglycerides, and uric acid). Systolic blood pressure was inversely correlated with SJL in both the control and diabetes groups. Whilst the results of the study do indicate associations between sleep timing variability and HbA1c, the direction of these relationships are at variance with some recent reports and indicate the need for future hypothesis-testing studies to further explore the impact of sleep timing variance on metabolic health.

Keywords: Sleep timing variability, type 2 diabetes, social jetlag, circadian, insulin resistance.

3.1 Introduction

As identified in chapter 1 DM is a leading global cause of mortality and morbidity, with a prevalence that continues to rise worldwide (Khan et al, 2020). T2D is associated with a number of debilitating complications including blindness, cardiovascular disease, end stage renal disease and non-traumatic limb amputations, and is also associated with high levels of disability-adjusted life years (Tracey et al., 2016). Increasingly, sleep is being recognised as an important factor for both disease risk and severity in T2D as well as T2D being potentially associated with elevated prevalence of sleep problems and disorders (Ogilvie & Patel, 2018; von Schantz et al., 2021). Our previous research as part of chapter 2 identified an association between SJL and poorer glycemic control in T2D (Kelly et al., 2020), although such findings are not ubiquitous (von Schnurbein et al., 2017; Mokhlesi et al., 2019; Reutrakul et al., 2013).

An area of emerging interest in circadian and sleep research is the role that irregular sleep timing may play in adverse health and quality of life outcomes (Bei et al., 2016; Duncan et al., 2016). Variability in sleep timing may reflect impairments of circadian or sleep homeostatic processes, may be related to other, better-studied measures such as subjective sleep quality and mean sleep duration, or may be reflective of social pressures on sleep (Bei et al., 2016). Greater sleep timing variability may be associated with greater "catch up" sleep at the weekend/work-free days, and such catch-up sleep has recently been proposed to be insufficient in ameliorating deleterious metabolic changes associated with short working-week sleep that in turn drives the need for catch-up sleep (Depner et al., 2019). A number of recent studies have indicated that sleep timing variability may be associated with disease outcomes in diabetes (type 1, Chontong et al, 2016; type 2, Brouwer et al., 2020) as well as increasing the risk for developing metabolic syndrome (Huang & Redline, 2019).

The current study sought to explore the relationships between various measures of actigraphically-determined sleep timing variability, and their associations with cardiometabolic markers in a group of healthy controls and a group of patients with uncomplicated, well-controlled T2D. The use of actigraphy provided objective measures of sleep, which goes beyond the self-reported measures reported in chapter

2. The study also sought to explore if there were differences between the control and T2D patients on a series of subjective and objective measures of sleep and circadian function. The primary aim of the study was to add to the burgeoning evidence base on the association of sleep timing variability and cardiometabolic health, and to generate specific hypotheses for future testing.

3.2 Methods

3.2.1 Participants

Thirty-one adult patients with T2D attending the outpatient annual review diabetes clinic at Connolly Hospital Blanchardstown, Dublin were recruited for this study. Twenty-seven age- and gender-matched controls were also recruited via poster advertising around the hospital campus and associated academic institutions. Participants were recruited from 2014 – 2015. Inclusion criteria were age >18 <66 years, and ability to provide informed consent. Participants in the T2D group were required to meet the 2011 WHO diagnostic criteria for diabetes mellitus (WHO, 2011). By the same criteria, participants enrolled to the control group required a HbA1c ≤42 mmol/mol, fasting plasma glucose <6.1 mmol/L, and plasma glucose 2-hours post oral ingestion of 75g glucose <7.8 mmol/L. Participants with suspected T1D, monogenic diabetes mellitus, or secondary causes of diabetes mellitus were excluded. The remaining exclusion criteria were chosen to limit confounding by factors with the potential to cause circadian rhythm disruption; participation in rotating shift work in the previous 5 years; a history of moderate-severe depression or other psychiatric illness; current use of drugs which affect sleep, such as sedatives or antidepressants; current habitual alcohol intake in excess of 20 units per week; significant medical co-morbidities which disrupt sleep, such as known obstructive sleep apnoea, or congestive cardiac failure. One participant with T2D was later excluded due to sleep schedules similar to that of a shift worker. Ethical approval for the study was granted by the Ethics Review Boards of Connolly Hospital, Dublin and the study fully conformed to the Declaration of Helsinki.

3.2.2 Clinical Metabolic Assessment

Participants presented to the Diabetes Day Centre in a fasting state. All participants commenced the protocol between 08:00 and 09:00. Fasting blood samples were drawn for glucose, insulin, LDL, HDL, triglycerides, total cholesterol, and HbA1c. Participantss then drank a solution containing 75g of glucose in the standard manner for an oral glucose tolerance test, with plasma glucose being repeated after 2-hours. During the two-hour interval participantss completed the study questionnaires and underwent a physical exam including height, weight, waist circumference, hip circumference, neck circumference and blood pressure measurement. History of

alcohol and nicotine use, as well as use of recreational drugs, was obtained. Insulin resistance was calculated based on the fasting plasma glucose and insulin levels using the HOMA-IR approximation formula (Matthews et al., 1985).

3.2.3 Subjective Sleep Measures

The MCTQ, a validated tool for assessing chronotype and SJL, was used to assess self-reported sleep timing on work nights and free nights (Zavada et al., 2005; Kantermann et al., 2015; Juda et al., 2013). Variables including chronotype and SJL were calculated in the standard way as previously described in chapter 2. Chronotype was measured as MSFsc an indicator of the underlying circadian phase and SJL reflects the difference in midsleep timing between work and free days. The Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep quality (Buysse et al., 1988). This was used in the standard way as previously described in chapter 2. Participants completed an Epworth Sleepiness Score questionnaire to assess daytime sleepiness (Johns, 1991). The Beck Depression Inventory II, a widely used instrument for detecting and measuring the severity of depression was administered to assess for occult depressive disorder (Wang & Gorenstein, 2013). Previous research has suggested that depressive disorder is associated with circadian disruption and is associated with poorer glucose control in T2D (Germain & Kupfer, 2008; Papelbaum et al., 2011).

3.2.4 Objective Sleep Measures

Continuous actigraphy, a validated non-invasive method of monitoring human rest/activity cycles which utilises an accelerometer to measure gross motor activity, provided objective measurement of the circadian rhythm (Ancoli-Israel et al., 2003). Participants wore a wrist worn actimetry sensor (*Actiwatch; CamnTech, UK*) for 6-10 days (mean duration of 9 days). The first and last days were excluded from subsequent analysis. Participants were also asked to keep a sleep diary to cross-reference actigraphic measures with contemporaneous self-reported sleep timing, some participants did not return the sleep diary (N = 15) and MotionWare software was used to determine sleep times (see section 3.2.5). Furthermore, any time the diary was shorter than the actigraphy recording MotionWare software was used to determine sleep times.

3.2.5 Actigraphy Calculations

Actigraphic data was analysed using non-parametric analysis of circadian rhythms and sleep analysis using the sleep algorithms of the MotionWare software (CamnTech, UK), cross-referenced to sleep diary data, to extract measures of sleep onset, sleep end, sleep efficiency, actual sleep time and assumed sleep time for each day for all participants. Periods during which the Actiwatch was omitted were removed from the analysis. From this variability in sleep onset, sleep end, sleep duration and midsleep timing was calculated by working out standard error of the mean over the number of days participants wore the actiwatch for. SJL from actigraphy was calculated as the difference in mean midsleep between participant-identified work and free days, only 42 participants returned this information, and this analysis was restricted to these individuals. Additional sleep variables were also calculated including actual sleep duration (total time spent in sleep), assumed sleep duration (time between first falling asleep and final wake time) and sleep efficiency (actual sleep duration as a percentage of total time spent in bed). Non-parametric circadian rhythm analysis was also performed which generates the following key variables that quantify the circadian rhythm: L5 - the average activity values during the least active 5 consecutive hours in a 24-hour period; M10 - the average activity during the most active 10 consecutive hours in a 24-hour period; Relative Amplitude - the difference between M10 and L5 normalised for an individual's activity; IS - interdaily stability which indicates how stable/consistent the rhythm is over several days; and IV - intradaily variability which indicates rhythm fragmentation on a given day (McGowan & Coogan, 2018).

3.2.6 Statistical Analysis

At the outset of the study, power calculations based on a 20% difference between groups on sleep timing variables, power of 0.8 and an alpha of 0.05 indicated that 30 participants per group would be a sufficient sample size to detect meaningful differences in sleep timing. Between group comparisons were performed by means of the independent samples t-test, where data was normally distributed and Mann Whitney U tests where the data was non normally distributed. Similarly, correlation analysis was conducted using Pearson's r or Spearman's rho depending on the normality of the data. As the approach employed was exploratory rather than

hypothesis testing, corrections for multiple comparisons were not undertaken. Statistical analysis was carried out using IBM SPSS version 25 (IBM Corporation, USA).

3.3 Results

3.3.1 Demographics and Clinical Features of the Study Sample.

Fifty-eight individuals participated in the study, 31 of whom had T2D and 27 normoglycaemic age and sex matched controls (Table 3.2). *One participant with T2D was removed due to unrealistic sleep times, leaving the final assessed sample at 57.* 50.9% of the participants were male. Mean BMI did not differ significantly between groups (controls mean = 28.76 ± 5.14 kg/m^2, T2DM mean = 31.78 ± 6.46 kg/m^2, $p = .058$), although there was a statistically significant difference in waist-hip ratio (control mean = 0.97 ± 0.09 vs 1.03 ± 0.06 for T2D, $p = .006$). One participant with T2D was excluded from the actigraphy analysis due to non-adherence to the experimental protocol (insufficient data collected) and one other was excluded from the biochemical analysis as they did not return samples. One control participant could not be phlebotomised and was thus excluded from analysis of biochemical data; any differences in sample size for analysis are noted throughout. All participants in the T2D group were receiving treatment with metformin, none were on insulin treatment, 29/31 were on lipid-lowering treatments and 19/31 were treated with anti-hypertensives; for the healthy control group, only one participant was on lipid-lowering therapy, and no other treatments were noted for this group (Table 3.1).

Table 3.1

Breakdown of the medication that individuals with T2D and controls were taking.

Metformin Any dose	**n/total (%)**	**29/31 (93.5%)**	**0/27 (0%)**	**<0.000**
Metformin TDD ≤1g	n/total (%)	3/29 (10.3%)	Na	Na
Metformin TDD >1g	n/total (%)	26/29 (89.7%)	Na	Na
Insulin Any dose	n/total (%)	0/31 (0%)	0/27 (0%)	Na
Lipid-lowering therapy Any dose	n/total (%)	29/31 (93.5%)	1/27 (3.7%)	<0.000
Anti-hypertensive therapy Any dose	n/total (%)	19/31 (61.3%)	0/27 (0%)	<0.000

No statistically significant differences were observed between controls and participants with T2D on sleepiness scores, PSQI scores, dietary quality, or depressive symptoms (Table 3.2). Patients with T2D did not differ in terms of MSFsc scored from the MCTQ but did have significantly greater MCTQ-determined SJL than controls (median of 42.6 minutes vs 22.8 minutes respectively; $p = 0.034$; Table 3.2 and Figure 3.1). Variables derived from the non-parametric analysis of circadian rhythms of actigraphic data (IS, IV, M10, L5 and RA) did not differ significantly between the control and T2D groups (Table 3.2). Actigraphic estimates of sleep duration, sleep efficiency and fragmentation also did not differ significantly between the control and T2D groups (Table 3.2). The Epworth sleepiness scale also did not differ significantly between groups suggesting that those with T2D did not show a significantly higher levels of daytime sleepiness a factor commonly associated with higher risk of sleep apnea, than controls.

Table 3.2

Demographic, glycemic, depressive, and both subjective and objective sleep variables in both groups.

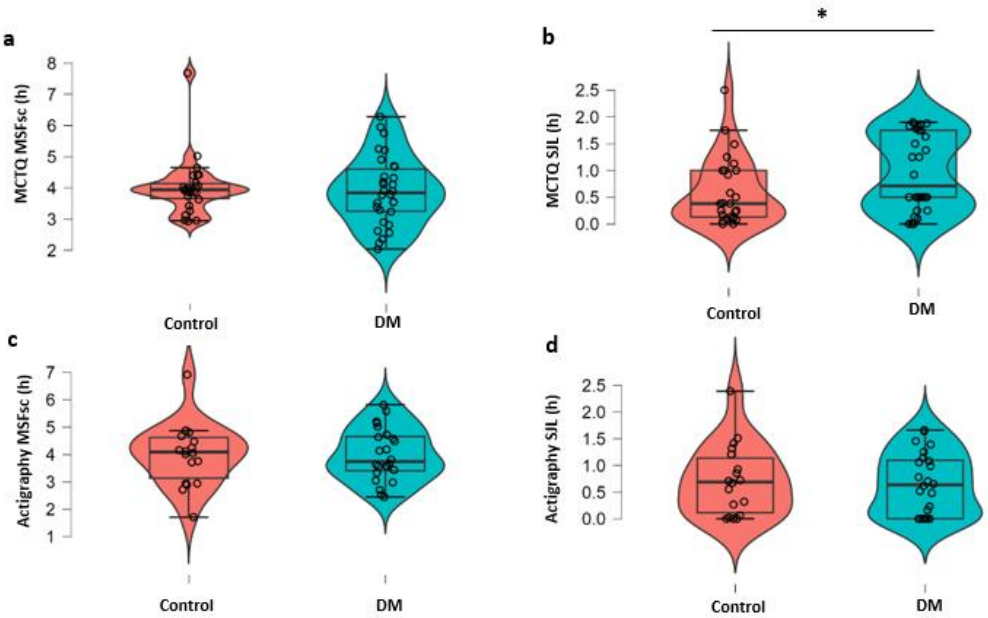
	Controls (N = 27)	**Diabetes Patients (N = 30)**	**p-value**
Age (years)	53.74 (6.57)	54.40 (5.11)	.678
BMI (kg/m^2)	28.76 (5.14)	31.78 (6.46)	.058
Gender (% male, N)	48.1 (13)	53.3 (16)	.696
Duration of Diabetes (years)	N/A	6.81 (3.02)	
Diastolic BP (mmhg)	78.62 (7.39) (N=26)	76.07 (11.17)	.313
Systolic BP (mmhg)	133.38 (12.86) (N=26)	127.87 (15.65)	.159
Average Alcohol (units/W)[a]	**9.00 (3-17)** (N=25)	**3.00 (0-10)**	***.030***
Fasting Glucose (mmol/L)[a]	**4.70 (4.50-5.00)**	**6.70 (5.90-7.80)** (N=29)	***<.001***
2 Hour OGTT Glucose (mmol/L)[a]	**4.85 (4.30-5.45)** (N=26)	**11.00 (8.30-14.30)** (N=29)	***<.001***
Fasting Insulin (mU/L)[a]	**8.19 (6.20-10.60)**	**18.50 (8.50-24.00)** (N=27)	***<.001***
2 Hour OGTT Insulin (mU/L)[a]	**20.00 (14.73-36.00)** (N=26)	**45.00 (27.00-80.00)** (N=27)	***.004***
HbA1c (mmol/mol)[a]	**36.00 (34.75-37.25)** (N=26)	**47.00 (44.00-54.50)** (N=29)	***<.001***
HOMA-IR[a]	**1.70 (1.30-2.29)**	**5.13 (2.52-7.63)** (N=27)	***<.001***
Total Cholesterol (mmol/L)[a]	**5.40 (4.50-5.90)**	**3.60 (3.30-4.09)** (N=28)	***<.001***
LDL (mmol/L)[a]	**3.24 (2.59-3.78)**	**1.71 (1.41-2.16)** (N=28)	***<.001***
HDL (mmol/L)[a]	1.34 (1.17-1.65)	1.22 (1.04-1.41) (N=28)	.141
Triglycerides (mmol/L)[a]	1.28 (0.96-2.15)	1.49 (1.12-1.90) (N=28)	.506
Uric Acid	317.04 (81.90) (N=26)	353.71 (72.50) (N=28)	.087
Depressive Symptoms[a]	3.50 (0.75-7.25) (N=26)	5 (2.75-9.25)	.195
Dietary Quality[a]	9 (8-10) (N=26)	8.5 (8-10)	.973
Subjective Sleep Measures	N=26	N=30	
EP Sleepiness[a]	3.50 (1.75-6.00)	4 (2.00-10.00)	.462
PSQI total[a]	3 (2.00-6.25)	4 (3.00-8.00)	.116
MSFsc(hours:minutes)[a]	3:56 (3:35-4:13) (N=26)	3:51 (3:09-4:41)	.706
SJL (hours:mins)[a]	**0:23 (0:07-1:00)** (N=26)	**0:43 (0:26-1:46)**	***.034***
Objective Sleep Measures	(N=27)	(N=29)	
IS (au)	.54 (.11)	.56 (.10)	.559
IV (au)	.80 (.17)	.72 (.20)	.108
M10 (counts)	19569.04 (5814.90)	19699.93 (5650.68)	.932
L5 (counts)[a]	816 (576-1137)	837 (604-1182)	.658
Relative Amplitude (au)[a]	.92 (.88-.94)	.91 (.88-.94)	.623
Actigraphy Sleep Onset	23:40 (0:57)	23:50 (0:53)	.471
Actigraphy Sleep End	07:42 (0:57)	07:52 (1:02)	.576
Actigraphy Actual Sleep Duration (hours:mins)	6:46 (0:49) (N=26)	6:51 (0:56)	.692
Actigraphy Assumed Sleep Duration (hours:mins)	8:02 (0:44) (N=26)	8:01 (0:51)	.904

Actigraphy Sleep efficiency (%)	81.48 (5.82) (N=26)	82.56 (5.51)	.485
Fragmentation Index[a]	30.55 (13.80) (N=26)	30.50 (13.80)	.566
Actigraphic Absolute SJL **(hours:mins)**	0:43 (0:40) (N=18)	0:40 (0:35) (N=24)	.752
Sleep Variability	(N=26)	(N=29)	
Sleep Onset Variability **(hours:mins)**	0:16 (0:07)	0:18 (0:08)	.523
Sleep End Variability **(hours:mins)** [a]	0:18 (0:14-0:21)	0:20 (0:13-0:27)	.458
Midsleep Variability **(hours:mins)** [a]	0:12 (0:10-0:17)	0:14 (0:11-0:21)	.328
Sleep Duration Variability **(hours:mins)** [a]	0:19 (0:14-0:24)	0:16 (0:13-0:20)	.372

Note. Mean ± standard deviation for normally distributed variables and median ± interquartile range for variables non normally distributed, marked with a superscript a. Independent samples t-tests/Mann Whitney U tests were conducted as appropriate. Chi-square test for independence used for assessing the relationship between categorical variables. Differences in sample size noted above.

Figure 3.1

Box-and-violin plots showing the distribution and median scores for MCTQ-derived MSFsc (a), MCTQ-derived SJL (b), Actigraphy-derived MSFsc (c) and Actigraphy-derived SJL (d) in the healthy control and T2D groups.



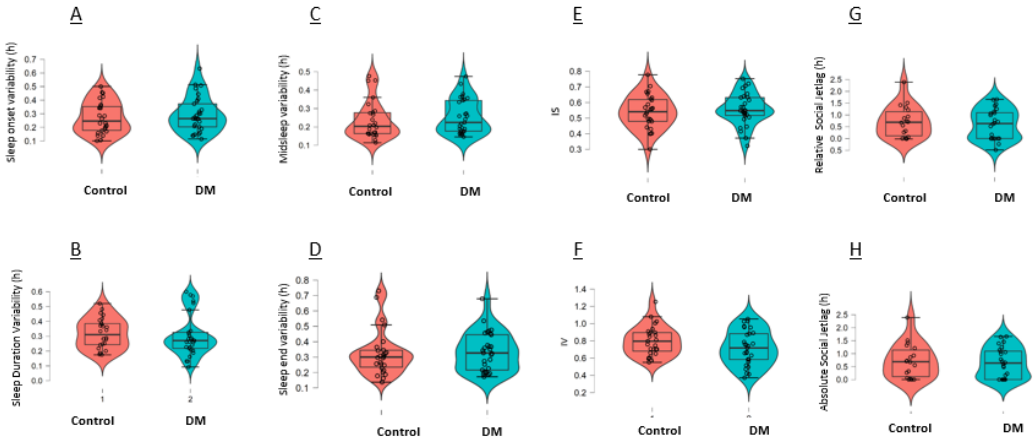
Note. * denotes p < .05 via Mann-Whitney U test (multiple comparisons are not corrected for).

3.3.2 Measures of Sleep Timing Variability

Measures of variability of sleep timing were calculated as standard error of the mean for sleep onset, sleep end, actual sleep duration and midsleep over the period for which the actiwatch was worn for each participant. None of these variables differed significantly between controls and participants with T2D (Table 3.2, Figure 3.2). The inter-correlations of variability on sleep onset, midsleep, sleep end and sleep duration are shown is Table 3.3; SEM in midsleep correlates strongly with both sleep onset and end, but not to sleep duration, whilst variability sleep onset and sleep end do not correlate significantly (Table 3.3). For measures of circadian sleep/wake variability, midsleep variability was weakly inversely correlated with IS (*rho* = -.324, *p* = .016) but there was no statistically significant relationship between midsleep variability and IV (*rho* = .158, *p* = .250; Table 3.3). Objective SJL was associated with sleep end variability (*rho* = .448, *p* = .003) but not with sleep duration, onset or midsleep variability (Table 3.3).

Figure 3.2

Box-and-violin plots showing the distribution and median scores for actigraphically-determined sleep parameters between the healthy control group and the T2D group.



Note. There were no statistically significant differences between groups on any of these measures. (A)-(D) sleep timing variability expressed as standard error of the mean for the period of actigraphy; (E-F) IS and IV expressed as arbitrary units; (G-H) SJL derived from actigraphy expressed as either relative amounts (G; earlier wake times on work free days compared to workdays expressed as negative values) and absolute values (H; all workday/work-free days differences expressed as positive values irrespective of the direction of the discrepancy).

Table 3.3

Correlation of SE SEM, SD SEM, SO SEM, MS SEM, SJL, and circadian variability (IS, IV) across the full study sample.

	SE SEM	SO SEM	MS SEM	SD SEM	IS	IV	Objective SJL
Full Cohort							
SE SEM	1						
SO SEM	rho = .217	1					
	p = .112						
MS SEM	**rho = .659*** **	**rho = .625*** **	1				
	p < .001	**p < .001**					
SD SEM	**rho = .477*** **	**rho = .491*** **	rho = .238	1			
	p < .001	**p < .001**	p =.081				
IS	**rho = -.480*** **	**rho = -.364** **	**rho = -.324***	**rho = -.360** **	1		
	p < .001	**p = .006**	**p = .016**	**p = .007**			
IV	**rho = .279***	rho = .139	rho = .158	rho = .134	**rho = -.580*** **	1	
	p = .039	p = .310	p = .250	p = .329	**p < .001**		
Objective	**rho = .448** **	rho = -.136	rho = .276	rho = .050	rho = -.146	rho = -.034	1
SJL	**p =.003**	p =.392	p = .077	p = .753	p = .355	p = .831	

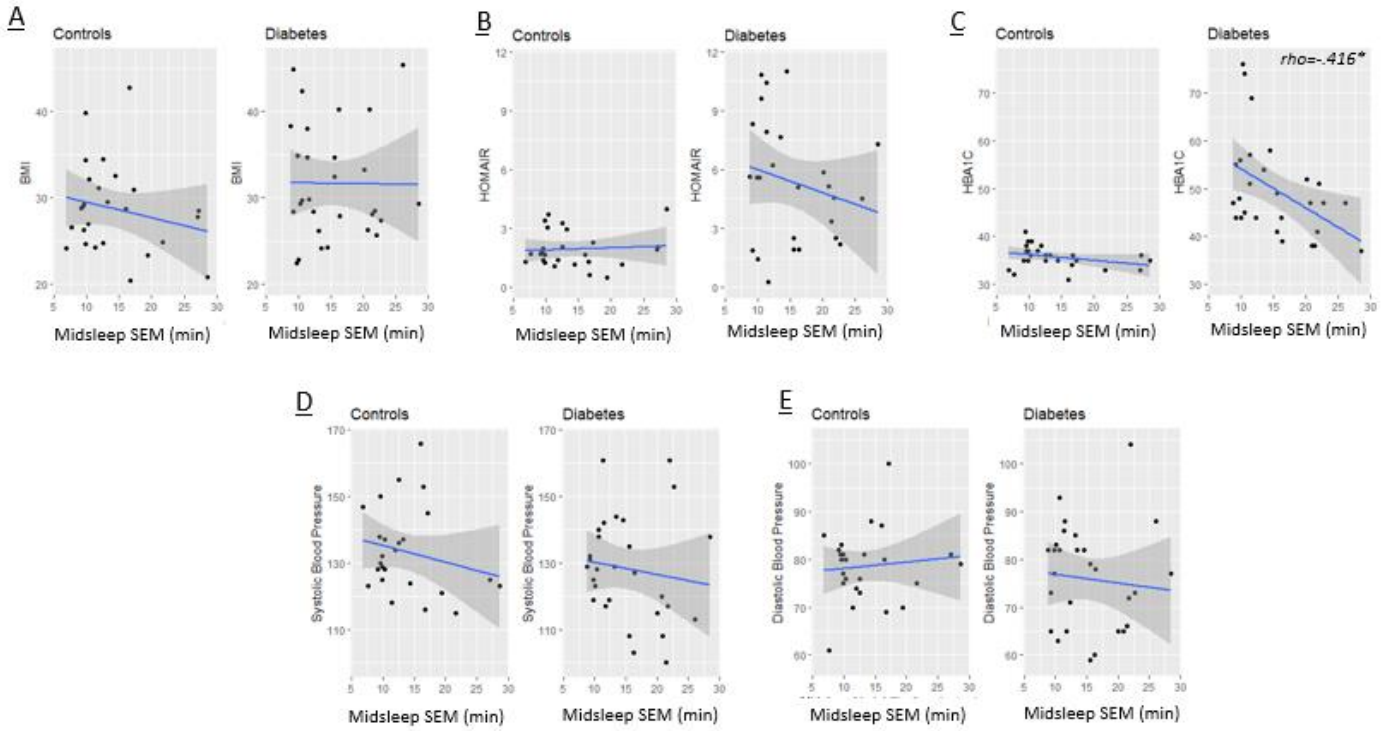
Note. N = 55 for all correlations of sleep timing variables, correlation between IS and IV N = 56, and those involving objective SJL N=42. p < .05 = *, p < .01 = **, p < .001 = ***

3.3.3 Sleep Timing Variability and Cardiometabolic Health

SEM in actigraphic midsleep was used as the primary indicator of sleep timing variability, as it showed a strong correlation with both sleep onset SEM and sleep offset SEM (Table 3.3). In patients with T2D there was a negative association between HbA1c and midsleep timing variability (*rho* = -.416, *p* = .027) while no significant association was observed in controls (*rho* = -.293, *p* = .155; Figure 3.3, Table 3.4). HbA1c also showed inverse correlations with sleep duration variability and sleep onset variability in T2D patients (Table 3.4), and positive association with PSQI scores in the T2D group (Table 3.4, Figure 3.4). HbA1c and BMI showed statistically significant positive correlations with IS in the control group (Table 3.4). HOMA-IR did not associate significantly with any of the sleep timing variability measures in either group (Table 3.4). Diastolic blood pressure also did not associate with any of the measures examined in either group, although higher systolic blood pressure associated with higher IS, lower IV and less actigraphically-determined SJL in controls and with less SJL also in the T2D group (Table 3.4, Figure 3.5).

Figure 3.3

Scatterplots illustrating the relationships between variability in the timing of midsleep and (A) BMI, (B) HOMA-IR, (C) HbA1c, (D) Systolic Blood Pressure and (E) Diastolic Blood Pressure.



Note. Only HbA1c in the T2D group showed a statistically significant association with Midsleep SEM. All correlation coefficients are expressed in Table 3.4 A/B.

Table 3.4 A

Associations between measures of sleep timing variability, circadian parameters, SJL, sleep quality and indicators of cardiometabolic health in controls.

A. Control Group

	HbA1c	HOMA-IR	BMI	SBP	DBP
MS SEM	rho = -.293, p = .155	rho = -.014, p = .946	rho = -.136, p = .506	rho = -.236, p =.255	rho = -.075, p =.721
SE SEM	rho = -.334, p = .103	rho = -.099, p = .631	rho = -.136, p =.506	**rho = -.509, p = .009**	rho = -.213, p = .306
SO SEM	rho = -.354, p = .082	rho = .018, p = .930	rho = -.097, p = .636	rho = .112, p = .593	rho = .145, p = .491
SD SEM	rho = -.147, p = .482	rho = .160, p= .436	rho = .074, p =.721	rho = .092, p = .663	rho = .069, p = .744
IS	**rho = .454, p = .020**	rho = .201, p = .315	**rho = .442, p = .021**	**rho = .393, p = .047**	rho = -.013, p = .948
IV	rho = -.184, p = .368	rho = -.197, p = .324	rho = -.379, p = .051	**rho = -.464, p = .017**	rho = .023, p = .913
SJL	rho = -.090, p = .731	rho = -.049, p = .848	rho = -.030, p = .906	**rho = -.517, p = .028**	rho = -.152, p = .546
PSQI	rho = -.249, p = .230	rho = .043, p = .834	rho = .016, p = .939	rho = -.028, p = .893	rho = -.113, p = .583

Table 3.4 B

Associations between measures of sleep timing variability, circadian parameters, SJL, sleep quality and indicators of cardiometabolic health in participants with T2D.

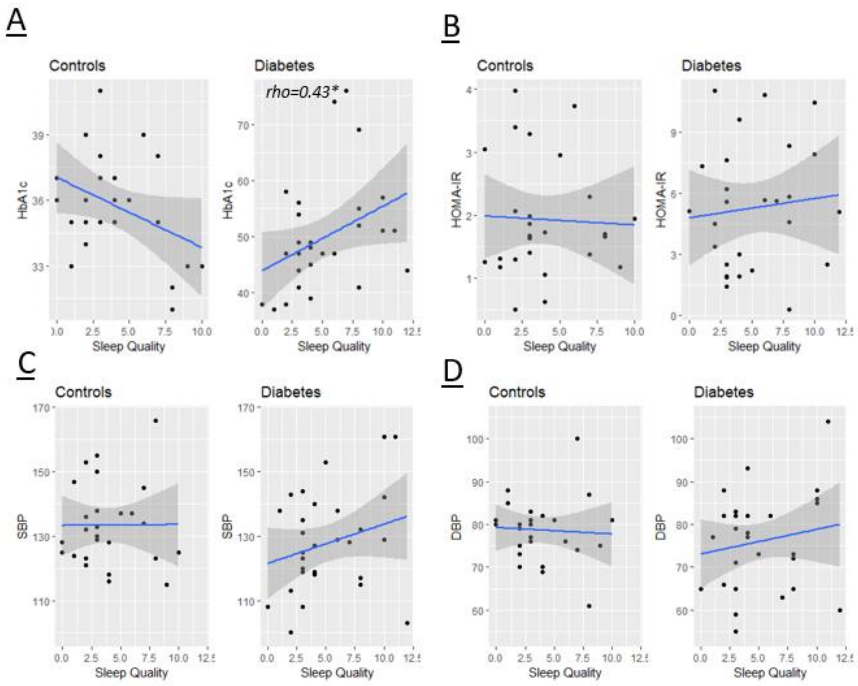
B. Diabetes Group

	HbA1c	HOMA-IR	BMI	SBP	DBP
MS SEM	**rho = -.416, p = .027**	rho = -.211, p =.302	rho = -.092, p = .636	rho = -.169, p = .380	rho = -.124, p = .521
SE SEM	rho = -.310, p = .108	rho = -.195, p = .339	rho = .076, p = .696	rho = -.243, p = .203	rho = -.122, p = .527
SO SEM	**rho = -.481, p = .010**	rho = -.269, p = .183	rho = .063, p = .747	rho = -.149, p = .440	rho = -.304, p = .108
SD SEM	**rho = -.398, p = .036**	rho = -.247, p = .223	rho = .303, p = .110	rho = -.123, p = .527	rho = -.230, p = .231
IS	rho = .162, p = .409	rho = .087, p = .673	rho = -.185, p = .337	rho = -.343, p = .068	rho = -.351, p = .062
IV	rho = -.028, p = .886	rho = -.064, p = .755	rho = .198, p = .304	rho = .164, p = .394	rho = .334, p = .076
SJL	rho = -.004, p = .986	rho = .055, p = .813	rho = .202, p = .345	**rho = -.473, p = .020**	rho = -.055, p = .799
PSQI	**rho = .429 p = .020**	rho = .087, p = .667	rho = .125, p = .512	rho = .207, p = .273	rho = .139, p = .465

SBP – systolic blood pressure; DBP – diastolic blood pressure. Analysis by Spearman's rho. (multiple comparisons are not corrected for).

Figure 3.4

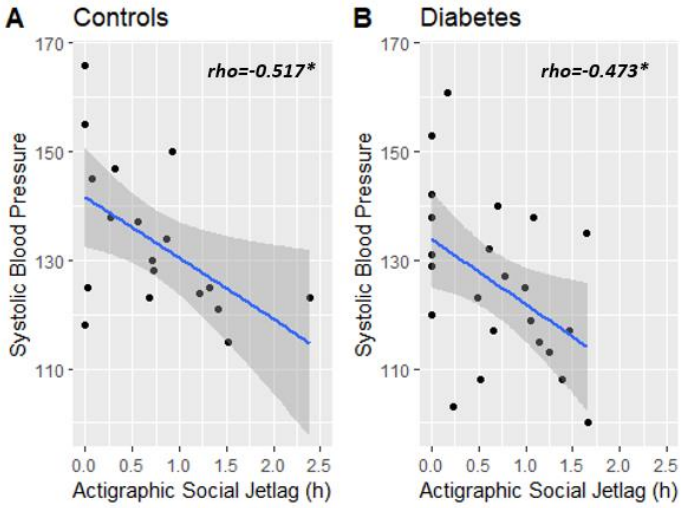
The association between sleep quality and HbA1c (A), HOMA-IR (B), SBP (C) and DBP (D) in controls and participants with T2D.



Note. Only HbA1c in the T2D group showed a statistically significant association with PSQI. All correlation coefficients are expressed in Table 3.4 A/B.

Figure 3.5

The association between SBP and actigraphically-determined SJL in both controls and those with T2D.



There were no significant associations noted between variability in midsleep or sleep duration and other metabolic markers (cholesterol, LDL, HDL, triglycerides, or uric acid) in the T2D group, and there was only one significant association in the control group (between sleep end variability and LDL, *rho* = -.427, *p* = .029; Table 3.5 A/B).

Table 3.5 A

Associations between measures of sleep timing variability, circadian parameters, SJL, sleep quality with blood metabolic biomarkers in controls.

A. Control Group

	Cholesterol	**LDL**	**HDL**	**Triglycerides**	**Uric Acid**
MS SEM	rho = -.243, p = .232	rho = -.280, p = .166	rho = .108, p = .599	rho = .060, p =.770	rho = -.162, p =.438
SE SEM	rho = -.357, p = .074	**rho = -.427, p = .029**	rho = .311, p =.122	rho = -.213, p = .295	rho = -.215, p = .303
SO SEM	rho = .051, p = .805	rho = .029, p = .889	rho = -.050, p = .809	rho = .306, p = .129	rho = -.006, p = .978
SD SEM	rho = .239, p = .239	rho = .189, p= .354	rho = .002, p =.993	rho = .220, p = .281	rho = .265, p = .200
IS	rho = .103, p = .610	rho = .255, p = .199	rho = -.217, p = .277	rho = -.117, p = .560	rho = -.023, p = .912
IV	rho = -.292, p = .139	rho = -.204, p = .308	rho = .185, p = .355	rho = -.268, p = .176	rho = -.224, p = .271
SJL	rho = -.001, p = .997	rho = .001, p = .997	rho = .126, p = .618	rho = .009, p = .971	rho = .133, p = .612
PSQI	rho = -.038, p = .854	rho = -.234, p = .251	rho = -.227, p = .265	rho = .388, p = .050	rho = -.039, p = .852

Table 3.5 B

Associations between measures of sleep timing variability, circadian parameters, SJL, sleep quality with blood metabolic biomarkers in participants with T2D.

B. Diabetes Group

	Cholesterol	LDL	HDL	Triglycerides	Uric Acid
MS SEM	rho = .102, p = .612	rho = .114, p = .571	rho = -.139, p = .489	rho = .084, p =.677	rho = -.081, p =.688
SE SEM	rho = .029, p = .884	rho = .216, p = .279	rho = -.107, p =.594	rho = .028, p = .889	rho = .187, p = .352
SO SEM	rho = .343, p = .080	rho = .330, p = .092	rho = -.101, p = .616	rho = .216, p = .279	rho = -.248, p = .212
SD SEM	rho = .314, p = .111	rho = .358, p= .066	rho = .094, p =.640	rho = .135, p = .501	rho = .091, p = .651
IS	rho = -.056, p = .780	rho = -.168, p = .403	rho = -.094, p = .642	rho = .001, p = .998	rho = -.060, p = .766
IV	rho = -.017, p = .935	rho = .179, p = .372	rho = -.258, p = .194	rho = -.059, p = .771	rho = .127, p = .527
SJL	rho = -.212, p = .343	rho = -.102, p = .651	rho = -.220, p = .325	rho = -.179, p = .424	rho = .374, p = .087
PSQI	rho = .343, p = .074	rho = .307, p = .111	rho = -.131, p = .506	rho = .147, p = .457	rho = .026, p = .894

3.4 Discussion

The current study explored putative associations between variability of sleep timing and cardiometabolic measures in a small group of healthy controls and participants with T2D. There have been recent indications that variability in sleep parameters, alongside the average values of sleep parameters, may be of consequence in homeostasis. For example, Chontong and colleagues (2016) have indicated that in T1D, greater standard deviation in sleep duration was associated with higher HbA1c levels and greater insulin requirement. In T2D an actigraphic study identified variability in sleep duration across one week as a predictor of HbA1c of equal or greater importance than average sleep duration or sleep efficiency (Brouwer et al., 2020). In another actigraphic study of a large cohort of older adults, a one hour increase in the variability of sleep onset over the course of a week was associated with a 23% increased risk of metabolic syndrome, and a one hour increase in sleep duration variability was associated with a 27% increased risk of metabolic syndrome (Huang & Redline, 2019). Taylor et al. (2016) report that greater variability in bedtime predicts more insulin resistance in a cross-sectional analysis of middle-aged women. In a small study of older adults with insomnia, increased variability in sleep duration was associated with higher HbA1c and variability in sleep onset associated with BMI (Baron et al., 2017). As such, alongside considerations such as average sleep duration, sleep fragmentation, subjective sleep quality and chronotype (Knutson et al., 2017), variability in day-to-day timing of sleep may be of importance for cardiometabolic health (Rosique-Esteban et al., 2018), although not all studies to date have supported this hypothesis (Slavish et al., 2019).

Previous work has indicated that SJL is associated with disease control in T2D (e.g., with HbA1c reported in chapter 2, by Kelly et al., 2020, and with blood pressure reported by Mokleshi et al., 2019). In our sample, SJL was only associated with sleep end variability, and not with variability in sleep onset or midsleep times, or with sleep duration variability. It may be the case, therefore, that these SJL and sleep timing variability factors represent different aspects of the sleep and circadian systems that may be of relevance for T2D, and as such should not be used interchangeably or assumed to be synonymous. Likewise, IV and IS measures from the non-parametric analysis of circadian rhythms indicate robustness and accuracy of circadian cycles driving sleep/wake timing and might be expected to be part associated with sleep

timing variability measures. In our data, IS (taken as an indicator of the entrainment of the circadian clock leading to more stable rhythms from day-to-day) showed moderate associations with all measures of sleep timing variability examined, whilst IV (taken as an indicator of within-day rhythm fragmentation) associated only with sleep end variability. Again, this data suggests that multiple measures of sleep timing variability and circadian rhythms are important, and all should be measured as they do not appear to be strongly collinear.

Our exploratory analysis does not reveal significant differences in the degree of sleep timing variability between the control and T2D groups, although the T2D group did self-report more SJL. Given that known sleep apnea was an exclusion criterion for the study, and that the patient group generally had well-controlled and uncomplicated disease, and that the control and T2D groups were reasonably well matched for BMI, perhaps such a finding is not surprising. Furthermore, we did not find any significant differences between the two groups on any of the actigraphic measures of sleep or circadian rhythms. In a cohort study of 2,156 adults, Abbott et al. (2019) reported no associations between IS or sleep timing from actigraphy and incident T2D or insulin resistance. Therefore, our current results indicate that T2D status may not be associated with group-wise differences in sleep timing variables in younger T2D patients with well controlled disease.

Within groups, it may be that sleep timing variability measures are associated with how well or poorly controlled the disease is. Brouwer et al. (2020) report that variability in sleep duration was the sleep factor most strongly associated with HbA1c in a cohort older than those in the current study (average age 66 vs. 54 years of age), and with poorer glycemic control than in the current study (mean HbA1c 57 vs 47 in the current study). In the study of Brouwer et al. (2020), variability in sleep duration accounted for 4.9% of the variance in HbA1c whilst variability in the timing of midsleep was also a significant predictor of HbA1c, accounting for 3.4% of the variance. Whitaker et al. (2018) report an association between higher sleep duration variability and higher HbA1c and this association was sensitive to waist circumference but not BMI. In an adult T1D sample, variability in both sleep duration and midsleep was also associated with HbA1c (with sleep duration variability being the stronger predictor; Chontong et al., 2016). Our results differ from these studies as we report inverse correlations between sleep timing variability and HbA1c. It is not immediately

apparent why less sleep timing variability might be associated with poorer glycemic control. In our sample, sleep timing variability did not strongly associate with average sleep duration, so we do not think that variability in sleep timing is a proxy for sleep duration, a factor that has been well described to be implicated in cardiometabolic health (Knutson et al., 2017). Another point of interest in the current results is that, while we did report associations between HbA1c and measures of sleep timing variability, no such associations were described for HOMA-IR, nor were such associations reported in any other study with T2D participants to date, to the best of our knowledge. As such, it may be important for future studies to tease out possible differential effects of sleep timing variability on other factors influencing HbA1c. Notably, previous research in a population not taking any insulin-related medications suggested that greater variability in mean sleep time was positively associated with HOMA-IR (Taylor et al., 2016).

Another factor revealed in our analysis is an association between lower social jetlag (derived from actigraphy) and greater systolic blood pressure in both control and T2D participants. Some previous studies have reported a lack of association between SJL and blood pressure (Mota et al., 2017; McMahon et al., 2019), although a recent study of pre-diabetes or untreated recently diagnosed T2D patients showed the opposite association between SJL and systolic blood pressure; greater SJL was associated with higher systolic blood pressure (Mokleshi et al., 2019). Clearly, the exact clinical composition of different study cohorts (e.g., in the use of antihypertensives) could explain discrepancies in reported associations between blood pressure and SJL. Information in statin use was not available for this group and is a limitation of the current study. In terms of our other measures of variability we did not find any associations between measures of sleep timing variability and blood pressure in our T2D patients, although less sleep end variability and higher IS was associated with higher systolic blood pressure in the control group. Suggesting again that more variability in wake times and less stable rhythms were associated with lower systolic lower blood pressure. Abbott et al. (2019) report an association between IS and blood pressure, although this effect disappears when shift-worker status was controlled for – shift workers were excluded in our study. The reasons for the associations found here with SJL and sleep timing again are not immediately clear and point to the

importance of understanding the psychosocial drivers of sleep timing and SJL in both healthy controls and patients with T2D.

A significant strength of this study was the length of actigraphy recording. In comparison to other studies, the average period of actigraphy used was longer (an average of 9 days) than many of similar studies in the same area (e.g., Brouwer et al., 2020 used 7 days actigraphy). There are a number of important caveats to the interpretation and evaluation of the current study. First, this is an exploratory study, and we did not seek to undertake hypothesis testing. The onset of the study in 2014 preceded the first publications on sleep timing variability in metabolic disease (Baron et al., 2017; Chontong et al., 2016; Whitaker et al., 2018), and as such we set out to explore the relationships between measures of sleep timing variability and cardiometabolic outcomes to generate hypotheses for subsequent testing. As the study was exploratory, we did not correct for multiple testing and as such the statistics presented should be interpreted appropriately. We also express variability in sleep timing as standard error of the mean, rather than standard deviation reported in other studies to control for variations in the numbers of usable actigraphy from each participant. Finally, the precise characteristics of the clinical sample is likely to be very significant in mediating putative associations between disease markers and sleep variables. The current T2D samples was a relatively young sample with well-controlled and uncomplicated disease with a low risk of undiagnosed moderate-to-severe sleep apnea.

In conclusion the present study highlights the need for future work to examine the social, behavioural, and physiological drivers of sleep timing variability in metabolic disease, as well as examining the impact of such factors on disease outcomes. Ultimately, the aim should be to identify potentially modifiable sleep behavioural factors for the improvement of disease outcomes and quality of life for the millions of patients worldwide living with T2D. The next chapter evaluates the potential associaton between SJL and stress to determine if stress could moderate any of the associations observed between circadian misalignment and metabolic health described so far.

Chapter 4:

The Association between Social Jetlag and Stress.

Abstract

Previous research has suggested that both SJL and stress may have negative impacts on metabolic and mental health. However, no studies have evaluated the relationship between these two variables in detail. This current study has two parts. Study one aimed to identify any association between SJL and general perceived stress (N = 400), and to to identify any association between SJL and work-related psychosocial stress in a subgroup of regular workers (N = 296). Study two investigated the association between SJL and the reaction to a physiological and socially evaluative stressor (N = 52). Both absolute (*rho* = .13, p = .012) and relative SJL (*rho* = .13, p = .011) showed a significant association with perceived stress in the bivariate analysis. However, when controlling for other sleep and demographic variables, this relationship no longer remained significant. PSQI (β = .52, p < .001), being female (β = .15, p < .001) and younger age (β = -.12, p = .019), were the only significant predictors.

In the subgroup of those with a regular work schedule, the relationship between SJL and the components of the job demand-control-support model were assessed. This model measures psychological demands, social support, and decision latitude in the workplace. SJL showed a bivariate association with decision latitude (*rho* = -.14, p = .019) but not psychological demands or social support. Once sleep and demographic variables were controlled for, this association was no longer significant. Earlier chronotype (β = - .14, p = .044) and shorter sleep duration (β = -.17, p = .011) were significant predictors of greater decision latitude. Additional analysis revealed that chronotype and SJL did not differ depending on job strain levels (high strain, low strain, active job, or passive job). In the stress reactivity task, SJL did not have any effect on a diastolic blood pressure, heart rate or and subjective stress ratings. There was a significant interaction between SJL and time during the task for systolic blood pressure whereby those with low and high SJL showed main effects of time, this was just slightly stronger in the low SJL group (p <.001, η^2= .79 for low; p < .001, η^2 = .57 for high). Overall SJL did not show any association with general perceived stress, or any component of the job demand-control-support model. SJL also did not predict stress reactivity. These findings suggests that it is unlikely that stress explains associations of SJL with health or vice versa in young adults.

Keywords: SJL, perceived stress, psychological demands, decision latitude, social support, stress reactivity.

4.1 Introduction

4.1.1 Stress

Stress is not a simple concept to define but forms a part of our everyday lives. Stress occurs when an individual does not have adequate resources to handle a given situation (Cohen et al., 2007; Lee et al., 2016). Stress may have an environmental, psychological, or biological basis and generally causes activation of our sympathetic nervous system (SNS) and hypothalamic pituitary adrenal (HPA) axis. This is adaptive over a short period of time, but prolonged stress has been shown to have a negative impact on mental and physical health (Cohen et al., 2007; Cooper et al., 2001).

Given the negative impact that stress and sleep timing can have on metabolic health, determining the association between these two variables is crucial. Section 4.1.5 evaluates the association between stress and sleep in more detail, however, this current study goes beyond this. It evaluates the association between stress and sleep timing in the general population to determine if they are related and how likely one may heighten or explain the effect of the other. This will guide future research on sleep timing and metabolic health in cohorts of individuals with metabolic diseases such as T2D. This research helps demonstrate how important it may be to control for additional variables such as stress when exploaring the relationship between circadian misalignment and health.

4.1.2 Subjective Measurement of Stress

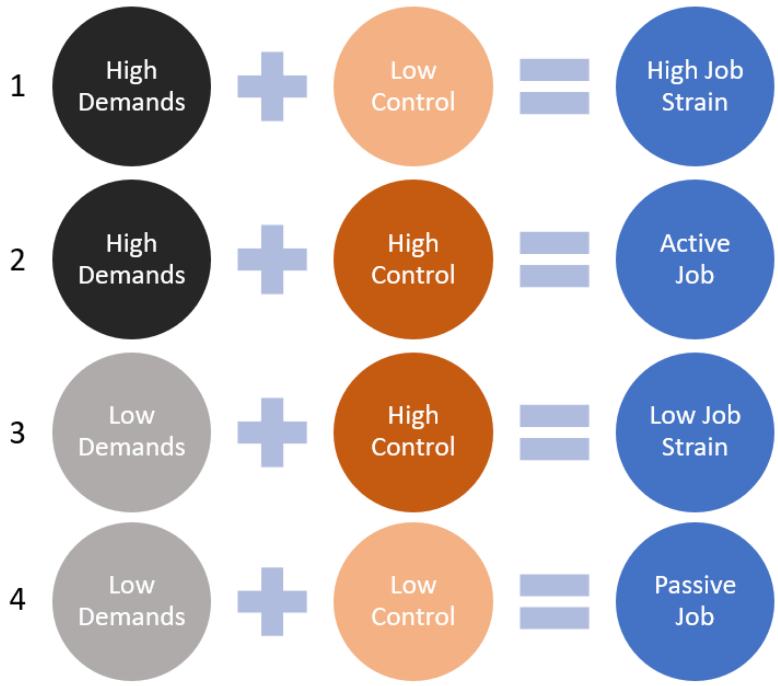
Stress can occur for numerous reasons and the perceived stress scale is useful as it provides a global measure of stress that can stem from different situations in people's lives rather than specific thoughts or behaviours (Cohen et al., 1983; Liu et al., 2020). This scale specifically captures an individual's perception of how overwhelmed life's circumstance make them feel (Croswell & Lockwood, 2020).

Stress is sometimes viewed as an unavoidable consequence of work life (Bell et al., 2012; Lee, Kim, et al., 2016) and since working-age adults in general spend 5 days per week at work, work-related stress is a very important variable to consider. While perceived stress should capture some of this in terms of overall stress, research on occupational stress often centres around the job demand-support-control model (Sanne et al., 2005). The demand-control model was initially proposed by Karasek and

the third component, support, was later added (Karasek, 1979; Mauss et al., 2018). The job content questionnaire (JCQ) was designed to measure these components and is a 49-item questionnaire (Karasek et al., 1998). The Swedish demand-control-support questionnaire (DCSQ) is a useful alternative with only 17 questions (Chungkham et al., 2013). This measure consists of three subscales: 'psychological demands' (captures arousal due to workload and work requirements), 'decision latitude' (captures both skill discretion and decision authority), and 'social support' (captures the support people feel at work; Sanne et al., 2005). People in general are said to have high job strain if they have low decision latitude and high psychological demands. Social support may then play a role in how stressful the situation is for the individual. This framework is useful for understanding the demands of work tasks and control over them (Chungkham et al., 2013). There are different measures of demands and control, but some previous studies have performed a median split on these scales which allowed them to categorise people into one of four groups depending on whether they had high or low demands in the workplace and high or low control over them (Karasek, 1979; Myllyntausta et al., 2021; see Figure 4.1). High demands and work intensity, lack of autonomy and poor work relationships have been identified as important psychosocial risk factors for health and wellbeing in the workplace (Eurofound, 2012).

Figure 4.1

Schematic diagram of the different stress models.



Note. 1 describes high strain which involves high demands and low control; 2 describes an active job which involves high demands and high control; 3 describes low job strain and involves low demands and high control; and 4 describes a passive job which involves low demands and low control.

4.1.3 Objective Measurement of Stress

Stress reactivity describes the response an individual has to a stressor. One of the most common methods for measuring stress reactivity in the laboratory is the cold pressor task (CPT; Schwabe et al., 2008). The CPT involves submerging an individual's hand in cold water to rapidly elicit a stress response, including increased BP and BPM (Minkley et al., 2014; Schwabe et al., 2008). The CPT is a very reliable method of increasing SNS activity but does not have as big of an impact on the HPA axis (Schwabe et al., 2008). The socially evaluated cold-pressor test (SECPT) is a development of the CPT and involves two additional aspects which are video recording and observation by the researcher (Schwabe et al., 2008; Schwabe & Schächinger, 2018). This is good for measuring stress reactivity as it combines a physiological stressor (cold water) and psychological stressor (social-evaluative

threat). The SECPT has been shown to elicit HPA axis activation as well as activation of the SNS, so it is preferrable over the CPT alone (Schwabe et al., 2008).

4.1.4 Stress and Metabolic Health

Kuo et al. (2019) identified increased risk of metabolic syndrome among people who displayed high stress, and that occupational stress had a stronger influence than general psychological stress. Diabetes onset and control may be affected by psychological stress via both changed behaviours and some physiological links (Lloyd et al., 2005). The number of stressful life experiences, taken as a measure of psychological stress, has previously been associated with undetected diabetes prevalence (Mooy et al., 2000). This research also found a weak association between psychological stress and levels of visceral fat (Mooy et al., 2000), which can lead to an increased risk of secondary metabolic consequences. Notably, fasting insulin concentration and visceral fat were not associated. Activation of the HPA axis with a perceived stressor could mediate this association between stress and diabetes as it leads to many endocrine abnormalities including high cortisol levels, altered catecholamine levels and low levels of sex steroids. This can block or reduce the effectiveness of insulin and lead to the derangement of metabolic control (Björntorp, 1997; Kelly & Ismail, 2015). Research in a healthy population for example demonstrated that increased epinephrine could reduce glucose tolerance (Hamburg et al., 1980). Stress may also increase unhealthy behaviours, for example physical inactivity, increased incidence of smoking and dietary changes, which then negatively impacts blood glucose control (Lloyd et al., 2005; Sendhilkumar et al., 2017). Mishra and colleagues (2020) found that individuals with severe stress and prediabetes had higher HbA1c than those with moderate or low stress. This suggests that stress may increase the risk of progressing from prediabetes to diabetes. Among those with already established diabetes those with severe stress had higher fasting blood glucose but not HbA1c than those with moderate or low stress (Mishra et al., 2020). However, perceived stress has previously been associated with poorer glycemic control in insulin dependent diabetes (Frenzel et al., 1988). Ruissen et al. (2021) identified an association between higher perceived stress and more difficulty with glycemic control during the COVID-19 pandemic. In addition, previous research has shown that stress management over a year led to a small but significant decrease in HbA1c levels (Surwit et al., 2002). The decrease was small (0.5%) however clinically important in

terms of secondary complications and their associated risk. Additional research by Zamani-Alavijeh et al. (2018) also suggested that stress management may lead to better glycemic control.

Research specifically on work-related psychosocial stress and diabetes is more varied. One study found an association between work stress and diabetes risk (Agardh et al., 2003). A meta-analysis of prospective cohort studies found no direct relationship between work-related stress and risk of T2D; however, in a subgroup analysis, greater job strain was associated with increased T2D risk in women (Sui et al., 2016). However, a previous systematic review and meta-analysis of prospective and cross-sectional studies found no link between work-stress or job strain and risk of T2D (Cosgrove et al., 2012). Some research also suggests that there is no relationship between work-related psychosocial stress and glycemic control among individuals with T2D (Annor et al., 2015). While the literature is inconclusive, it is possible that stress can affect metabolic health. There are also many serious consequences of living against the circadian clock as discussed in chapter 1. Previous research presented in this thesis found an association between greater SJL and greater HbA1c in people with T2D (chapter 2 / Kelly et al., 2020). Many of these studies control for a number of important covariates but do not consider the role that stress may have.

4.1.5 Stress and Sleep

Since SJL is an indicator of chronic circadian disruption and much of our biology is regulated by the circadian clock, SJL may be a persistent physiological stressor (Sűdy et al., 2019). Beyond physiological stress it is important to consider the potential relationship between SJL and psychological stress, given the relationship between both psychological stress and SJL with metabolic health (Kelly et al., 2020; Kuo et al., 2019). Eveningness has been associated with increased perceived stress and those with greater eveningness preference may also be experiencing more SJL (Wittmann et al., 2006; You et al., 2020). Further to this, SJL has been associated with some mood related disorders including increased depressive symptoms, indicating another potential link between stress and sleep (Levandovski et al., 2011; Okajima et al., 2021). However, one study assessing bruxism failed to identify any association between perceived stress and either chronotype or SJL in university students (Jokubauskas et al., 2019).

High job strain as a measure of work stress has been linked to sleep in the past with a lot of the research focusing on the association with poorer sleep quality (Halonen et al., 2017; Leitaru et al., 2019). Less research on the association between job strain and other sleep characteristics including duration and timing has been conducted and the findings have been mixed. Dahlgren et al. (2005) demonstrated that employees experienced shorter sleep duration on a workweek with high strain when compared to a workweek with low strain. Interestingly, sleep onset and end did not vary between the weeks. Further research by Karhula et al. (2013) compared sleep duration among shift workers with high and low strain and found no significant differences. A recent study on older public sector employees in Finland demonstrated that sleep duration on workdays did not differ between job strain groups but that those with high strain slept for longer and later on free days (Myllyntausta et al., 2021). Another recent study with a different measure of job stress found an association between greater SJL and job stress in Japan (Takaesu et al., 2021). In this study, short workday sleep duration, short and long free day sleep duration were also associated with job stress. Interestingly, SJL had an impact when controlling for chronotype, as measured by MSFsc (Takaesu et al., 2021).

In terms of the physiological markers of stress and stress reactivity Roeser and colleagues (2012) found that evening orientation, as measured by the MEQ, was associated with higher systolic BP and higher BPM both at baseline and during a mental stress test. No association with diastolic BP was observed. Like the study on perceived stress above, this research did not assess average midsleep or SJL when examining stress reactivity and the SJL that evening chronotypes may experience should be considered (You et al., 2020). BP has been increased by circadian misalignment in both shift workers and non-shift workers (Morris et al., 2016; Morris et al., 2017; Scheer et al., 2009). Morris and colleagues (2017) induced a shift work protocol in the laboratory and 24-h systolic BP increased by 1.4 mmHg and 24-h diastolic BP increased by 0.8 mmHg. This research suggests that circadian misalignment may be a risk factor for increased BP, however it does not cover if individuals with more circadian misalignment actually react more to stressors in their lives. Research on stress reactivity in Japan as measured via self-report found no association with SJL (Adachi et al., 2021). This was limited by the questions used to assess sleep timing.

The overall aim of this research was to assess the relationship between SJL and stress. The research had two parts: Study 1 and Study 2. The aim of Study 1 was to assess the association between SJL and both perceived and work-related stress. A number of objectives were set out to achieve this aim. The first objective was to determine if there was any cross-sectional relationship between SJL and perceived stress, and whether SJL predicted variance in perceived stress levels, controlling for other demographic and sleep related variables. The second objective was based on a smaller subset of participants, excluding students and irregular workers. This was to determine whether SJL was associated with any of the demand-control-support aspects of this job strain model, and if so, could SJL predict variance in these measures beyond demographic and other sleep related variables. Participants were also put into groups depending on the level of job strain experienced and differences between groups were evaluated. The aim of Study 2 was to determine whether SJL influenced stress reactivity in the SECPT. For Study 1 the hypothesis were as follows:

1. Greater SJL will predict higher perceived stress levels.
2. Greater SJL will predict higher psychological demands, and lower decision latitude in workers.

Study 2 was exploratory rather than confirmatory, so no specific hypothesis were developed here.

4.2 Study 1: *Cross-Sectional Association between Social Jetlag and Stress (both Perceived and Work-Related).*

4.3 Methods

4.3.1 Participants

Between October 2019 and October 2020, 468 individuals completed an online questionnaire. Due to the COVID-19 pandemic no responses were collected between March and September 2020 in order to control for the changing nature of the work environment and the impact of the national lockdowns. Once this period of time had passed and individuals had climatised to this new culture, recruitment recommenced. Fifty-seven percent of the sample (N = 228) was collected before March 2020, and forty-three percent of the sample (N = 172) was collected in September/October 2020. Of these responses, 17 participants were excluded due to work schedules at night, 49 further responses were excluded due to either alarm clock use on free days or stating no free days, two further participants were excluded due to unrealistic values being provided. The final sample with usable data was 400. Participants were aged between 18 and 69 years old (M = 33.63, SD = 12.80). This study was approved by the Biological Research Ethics Sub-Committee at Maynooth University and all research was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants as they were required to consent in order to proceed to the surveys.

4.3.2 Measures

All participants reported their age (in years), gender, current job-status (employed/unemployed/retired/student) and whether they worked full-time or part-time. Commute time to work and normal work start and end times were assessed. Participants had to self-select an occupation from a drop-down menu guided by the International Standard Classification of Occupations (ISCO, 2008). Participants were also presented with an open-ended box to describe their job so that classifications could be checked by the researcher. This classification system was then used to group participants as full-time workers, students, or non-traditional workers (i.e., homemaker, carers) where they may not have had regular hours. Shift working status was also assessed and those working nightshifts were excluded.

The MCTQ was used to provide an estimate of participants' underlying circadian phase of entrainment and SJL (Roenneberg et al., 2003). This instrument asks about typical sleep behaviour on both workdays and free days over the previous month and has two sections with illustrative diagrams. This was previously described in detail in chapter 2 (section 2.2.3). The key variables of interest in this study were SDweek, reflecting average sleep duration across the week; MSFsc, an indicator of chronotype; relative SJL and absolute SJL. The PSQI as described in chapter 2 (section 2.2.3), was used to evaluate subjective sleep quality over the previous month. The PSQI was primarily analysed as a continuous variable. In order to visualise good and poor sleep quality in the sample those with a score of less than or equal to 6 were classed as having good sleep quality and those with a score of more than 6 were classed as having poor sleep quality (Manzar et al., 2015). Previous validation of the PSQI revealed a Cronbach's α of .83, making it a good self-reported measure of sleep quality (Buysse et al., 1989).

The perceived stress scale (PSS) measures the perception of stress by assessing individual's feelings and thoughts over the previous month (Cohen et al., 1983). This is to determine how various situations impact our global stress levels. The PSS-10 was used over the PSS-14 as it has slightly superior psychometric properties and fewer questions reducing the burden on respondent's time (Cohen & Williamstown, 1988; Lee, 2012). The PSS-10 has 10 items that are all rated on a 5-point Likert scale from 0 (never) to 4 (very often). Items 4,5,7,8 were positively worded and were reversed before the total score was calculated, and total scores can range from 0-40. Higher total scores indicate higher psychological stress (Cohen & Janicki-Deverts, 2012). The Cronbach's α of this scale was evaluated in 12 studies and found to be > .70 in each making it a reliable measure (Lee, 2012). An example of a negatively worded item included: "In the last month, how often have you been upset because of something that happened unexpectedly?". An example of a positively worded items that must be reversed included: "In the last month, how often have you felt confident about your ability to handle your personal problems?".

In addition to the PSS the demand control support questionnaire (DCSQ) was utilised to measure work stress or job strain more specifically among participants who identified as working (N = 296). The DCSQ is a 17-item questionnaire that measures three subscales; psychological demands (5 items), decision latitude (6 items), and

social support at work (6 items; Sanne et al., 2005; Chungkham et al., 2013; Mauss et al., 2018). Although some research argues that decision latitude is made up of two sub-components: skill discretion and decision authority (Chungkham et al., 2013), they tend to correlate highly, and it was assessed as a single component in this study as many other studies have (Mauss et al., 2018). The English version of this scale was obtained from a previous study by Chungkham and colleagues (2013). Each item on this scale was rated on a four-point likert scale. Items on decision latitude and psychological demands were all rated from 1 often to 4 never/almost never while items from social support at work were all rated on a similar likert scale but from 1 strongly agree to 4 strongly disagree. All scores except item 4 on enough time and 9 on repetitive work were reversed and totalled so that higher scores indicated greater psychological demands, greater decision latitude and greater social support at work (Chungkham et al., 2013). This is how responses in the Swedish longitudinal occupational survey of health (SLOSH) were scored and follows the instructions outlined by Chungkham et al. (2013). This scale was validated by Mauss et al. (2018) however in the validation study all 17 items were presented as statements and individuals were asked to rate them all on a four-point likert scale from strongly disagree to strongly agree. Items 4 and 9 were reversed and similarly higher scores indicated higher psychological demands, greater decision latitude and greater social support at work. All scales in our study had acceptable internal consistency with a Cronbach's α of .84, .71, and .71 obtained for social support, decision latitude and psychological demands, respectively. Mauss et al. (2018) reported a Cronbach's α of .83, .77 and .72 which is very similar to this current study. Therefore, high convergency between reliability was observed despite slight variations in phrasing of likert scale options.

4.3.3 Procedure

Convenience sampling was used as participants were recruited through social media, flyers at Maynooth University, and posts online. Some students were also recruited through the department of psychology's participant pool. The department of psychology's participant pool is made up of all full-time psychology students from Maynooth University in their second year of study. These students must complete three hours of psychology experiments of their choosing or complete an essay as an alternative. The students can choose from all studies being conducted in the

department and for this particular study received 30 minutes of experience with a relevant study. Once the survey was complete the researcher provided a signed participation sheet. Individuals had to be at least 18 years old to participate with both work and free days. When potential participants opened the survey link, they were first presented with detailed information on the study which covered the purpose of the study, confidentiality, and data handling policies. Email addresses of the researcher and the project supervisor were also included in the event that participants had any further questions. Anyone under the age of 18 was automatically directed to the end of the survey. After consenting to proceed, participants were first asked some demographic details, information on work schedule and occupation before being directed onto the surveys. The MCTQ was presented first, followed by the PSQI, the 10-item PSS, and the 17-item DCSQ. All these questionnaires had to be completed in one session and the participants required around 15 minutes to complete the surveys. The online Qualtrics database only saved responses that were 100% complete.

4.3.4 Data analysis

Phase 1 – Descriptive statistics and assessment of normality. Descriptive analyses were conducted first. All variables were visually inspected, and the Kolmogorov Smirnov statistic was also consulted to determine normality.

Phase 2 – Group differences and correlations. One-way ANOVAS/Kruskal Wallis tests were used to examine differences between groups (student, employed, career/homemaker) for demographic, sleep and circadian variables depending on normality. When assessing the initial relationship between variables, including measures of stress (perceived stress in the full sample and components of the job demand-control support model in the subgroup of employed participants) and circadian variables including chronotype and SJL, Pearson's r was used for normally distributed variables while Spearman's rho was used when the data was non-normally distributed.

Phase 3 – Regressions. Hierarchal regression was conducted to determine the association between absolute SJL and perceived stress levels, after controlling for demographics and other sleep related variables. Absolute SJL was investigated over relative as this is the most commonly assessed version of the variable in terms of outcome measures (Roenneberg et al., 2012; Roenneberg et al., 2019). A sub-group

analysis of individuals who were not students was conducted in order to test the measures of work stress and their potential associations with sleep and circadian variables. Multiple linear regression was used here with the three aspects of the demand-support-control model being the CVs.

Phase 4 – Categorisation of SJL and groupwise analysis. SJL was next examined as a categorical measure and differences between stress, demographic and other sleep variables were investigated using either one-way ANOVAs or Kruskal-Wallis tests depending on normality.

Phase 5 – Categorisation of job strain and groupwise analysis. Job strain as a categorical measure was then investigated by carrying out a median split on psychological demands and decision latitude and then putting participants into one of the four categories outlined in Figure 4.1. Differences in all MCTQ and PSQI measured sleep variables were then investigated using Kruskal-Wallis tests. All analysis were conducted on SPSS version 26. JASP version 0.14.1.0 statistics and RStudio ("ggplot2") were used to make some of the figures.

4.3.5 Sample size calculation

Daniel Sopher online statistics calculator was utilised to guide the minimum sample size required for the hierarchal regression analysis. In order to detect a small effect size (.02) of the predictor in our second block, in this case absolute SJL, a suggested minimum sample size was 390. This was with an alpha level of .05 and a power of .8. Our sample of 400 was therefore sufficient. Daniel Sopher online sample size calculator was utilised to determine the minimum sample required for multiple linear regression in order to identify a medium effect (.15), at alpha level < .05 with 90% power using 7 predictors, a sample of 129 was required. We had 296 participants in this group. The online calculator can be accessed here: https://www.danielsoper.com/statcalc/calculator.aspx?id=16 .

4.4 Results

4.4.1 Descriptives

There were 400 usable complete responses in this study. Of these 80% were female and the mean age was 33.63 (*SD* = 12.80). There was a range of students, either undergraduate or postgraduate (22.5%), workers (74%), and individuals not in conventional 9-5 employment, usually caring for a child or elderly relative (3.5%), who participated. The average age of workers was 35.99 years (*SD* = 12.42) and 78% of the sample identified as females. Of those employed the majority identified as professionals (58.4%), followed by those working in sales and services (16.9%), then administration (12.2%), then assistant professionals (8.1%) and then a group who engaged in manual labour (i.e., farming, construction; 4.4%). See Table 4.1 for details on all variables.

4.4.2 MCTQ-Derived Sleep and Circadian Characteristics

SJL, which captures the misalignment between workday and free day sleep timing patterns, was calculated in both relative and absolute terms. Median relative SJL was 1:05 (*IQR* = 1:12), this ranged from negative 1:32 to positive 4:30; however, only 4.5% of the sample displayed negative misalignment. This suggests only a small minority of the sample experienced phase delays when moving from their free day schedules to their workday schedules and that most of the sample experienced phase advances when moving from a free day to a workday. Median absolute SJL was 1:08 (*IQR* = 1:10; see Table 4.1). See Figure 4.2 for distribution of both. Absolute SJL was grouped and 47.3% displayed less than one hour, 38.5% displayed 1-2 hours and 14.2% displayed more than 2 hours SJL. Notably, students showed no negative SJL and as such their relative and absolute SJL were equal (ranging from 0 – 3.71 hours).

Table 4.1

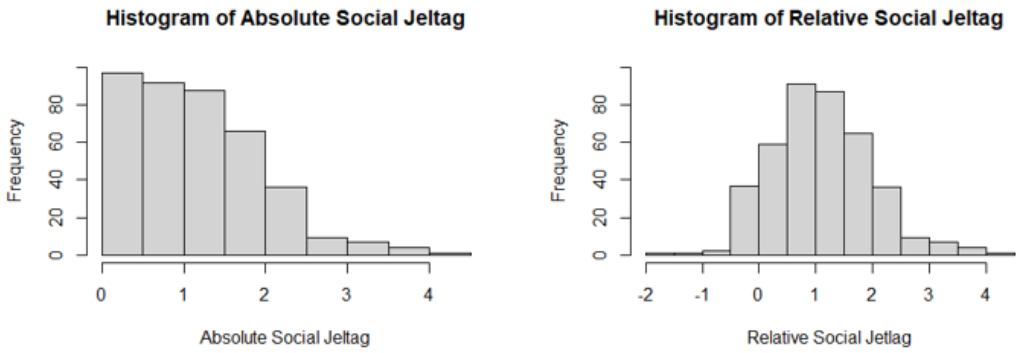
Descriptive statistics of the samples demographic and sleep related variables.

Variable	Mean (SD) / N (%)
Sample size (N)	400
Age	33.63 (12.80)
Sex	
Male	80 (20%)
Female	320 (80%)
Work Group	
Students	90 (22.5%)
Workers	296 (74%)
Non-traditional workers	14 (3.5%)
Worker sub-divisions	
Professionals	173 (58.4%)
Sales/Services	50 (16.9%)
Administration	36 (12.2%)
Assistant professionals	24 (8.1%)
Manual labour	13 (4.4%)
Work Length[a]	
Full Sample (N = 389)	8.50 (1.50)
Traditional workers (N = 290)	8.50 (1.33)
Covid	
Pre-pandemic	228 (57%)
Post-lockdown	172 (43%)
Sleep Quality	6 (5)
SDw[a]	7:27 (1:25)
SDf[a]	8:25 (1:30)
SDweek	7:42 (1:04)
MSFsc	4:18 (1:11)
Absolute SJL[a]	1:08 (1:10)
Relative SJL[a]	1:05 (1:12)

Note. Superscript a indicates that the variable was not normally distributed. Continuous data are mean ± (SD) or median (IQR) depending on normality. Categorical variables are presented as N (%).

Figure 4.2

Distribution of absolute and relative social jetlag.

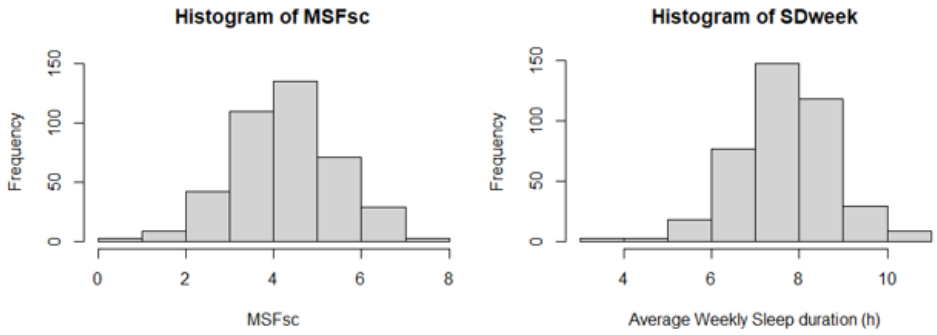


Note. The figure on the left depicts the total amount of absolute SJL (h). The figure on the right demonstrates the relative SJL (h) of the sample. As can be observed the majority of the sample are displaying positive SJL. SJL is displayed here in hours.

The mean MSFsc of the sample was 4:18 am (*SD* = 1:11) and ranged between 00:29 and 08:00 am. Participants reported sleeping an average 7 hours and 42 minutes per night (*SD* = 1:04). Both MSFsc and average sleep duration were normally distributed (Kolmogorov-Smirnov statistic = .200 & .166 respectively; see Figure 4.3). Breakdown of these variables in each group can be observed in Table 4.2. Students were significantly younger, had more relative and absolute SJL, later MSFsc but also the longest average weekly sleep duration.

Figure 4.3

Distribution of MSFsc and average weekly sleep duration.



Note. Histogram on the left depicts the distribution of chronotypes as measured by MSFsc (h) and the histogram on the right demonstrates the average sleep duration in hours across the week.

Table 4.2

Descriptive analysis of the sample in each group (students, workers, and homemakers/carers).

Variable name	1. Students (N = 90)	2. Employed (N = 296)	3.Carer/ Homemaker (N = 14)	Sig
Age	23.67 (0.77)*2,3	35.99 (0.72)*1,3	47.79 (3.15)*1,2	<.*001*
Gender (%, male)	15.6	22.0	7.1	.195
Relative SJL [a]	1:19 (0:55)*2,3	1:00 (1:10)*1,3	0:15 (1:15)*1,2	<.*001*
Absolute SJL [a]	1:19 (0:55)*2,3	1:03 (1:10)*1,3	0:15 (1:04)*1,2	<.*001*
MSFsc	5:06 (0:06)*2,3	4:04 (0:04)*1	4:05 (0:19)*1	<.*001*
Average Sleep Duration	8:01 (0:06)*2,3	7:38 (0:04)*1	7:04 (0:16)*1	<.*001*

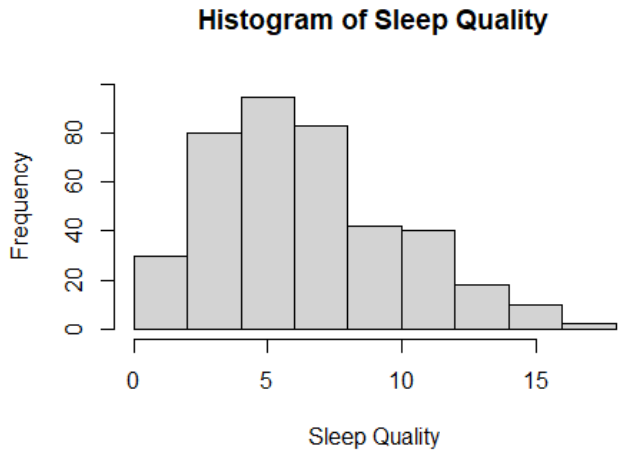
Note. Superscript a indicates that the variable was not normally distributed. Data are mean ± (SE) or median (IQR) depending on normality. SJL, MSFsc and average sleep duration reported in hours and minutes.

4.4.3 PSQI-Derived Sleep Quality

PSQI scores were not normally distributed (Kolmogorov Smirnov statistic < .001, see Figure 4.4). Median PSQI was 6.00 (*IQR* = 5.00, *range* = 0-17), with 48.8% of the sample being classified as poor sleepers (PSQI > 6). PSQI component scores displayed acceptable level of reliability (Cronbach's α = .75).

Figure 4.4

Distribution of sleep quality in the current sample.



Note. Histogram depicts the distribution of PSQI scores indicative of sleep quality in the current sample.

Later chronotype was associated with greater relative SJL (*rho* = .52, *p* < .001), and absolute SJL (*rho* = .49, *p* <.001) but not sleep quality (*rho* = .08, *p* = .103). Neither relative SJL (*rho* = .05, *p* = .360) nor absolute SJL (*rho* = .06, *p* = .243) were associated with sleep quality.

4.4.4 Perceived Stress in the Sample

The PSS scale gave a measure of overall psychological stress which was normally distributed in the final sample. Mean PSS was 18.07 (*SD* = 6.81), which is slightly under half the maximum score. This scale showed good reliability (Cronbach's α = .89). T-test analysis revealed that PSS was, on average, higher in females (*M* = 18.78, *SE* = 0.37) than males (*M* = 15.21, *SE* = 0.73), *t*(398) = -4.284, *p* < .001, Cohen's *d* = .54. The results of the one-way ANOVA revealed that PSS also

differed between 'work' category. Students (M = 20.14, SE = 0.65) reported higher PSS that workers (M = 17.39, SE = 0.39) but not non-traditional workers (M = 19.07, SE = 2.43), $F(2,397) = 5.96$, $p = .003$, $\eta^2 = .029$.

4.4.5 Assessing the Association between Perceived Stress and SJL

Perceived stress was weakly and positively associated with relative SJL (*rho* = .127, $p = .011$) and absolute SJL (*rho* = .126, $p = .012$). Later chronotype was also positively associated with perceived stress (*rho* = .182, $p < .001$; see Figure 4.5). These associations can be observed in Table 4.3 in addition to the associations in each of the groups (see also Figure 4.5). Higher levels of perceived stress were associated with poorer sleep quality in the full sample (*rho* = .54, $p < .001$; see Figure 4.5) and each of the three work categories (see Table 4.3).

Figure 4.5

*Bivariate associations between absolute SJL (A), relative SJL (B), MSFsc (C), PSQI (D), free day sleep duration (E), workday sleep duration (F), and average sleep duration across the week (G) with perceived stress. * = p < .05, ** = p < .01 *** = p < .001. The contour lines are "heat" coloured from green to red which correspond with the plotting density.*

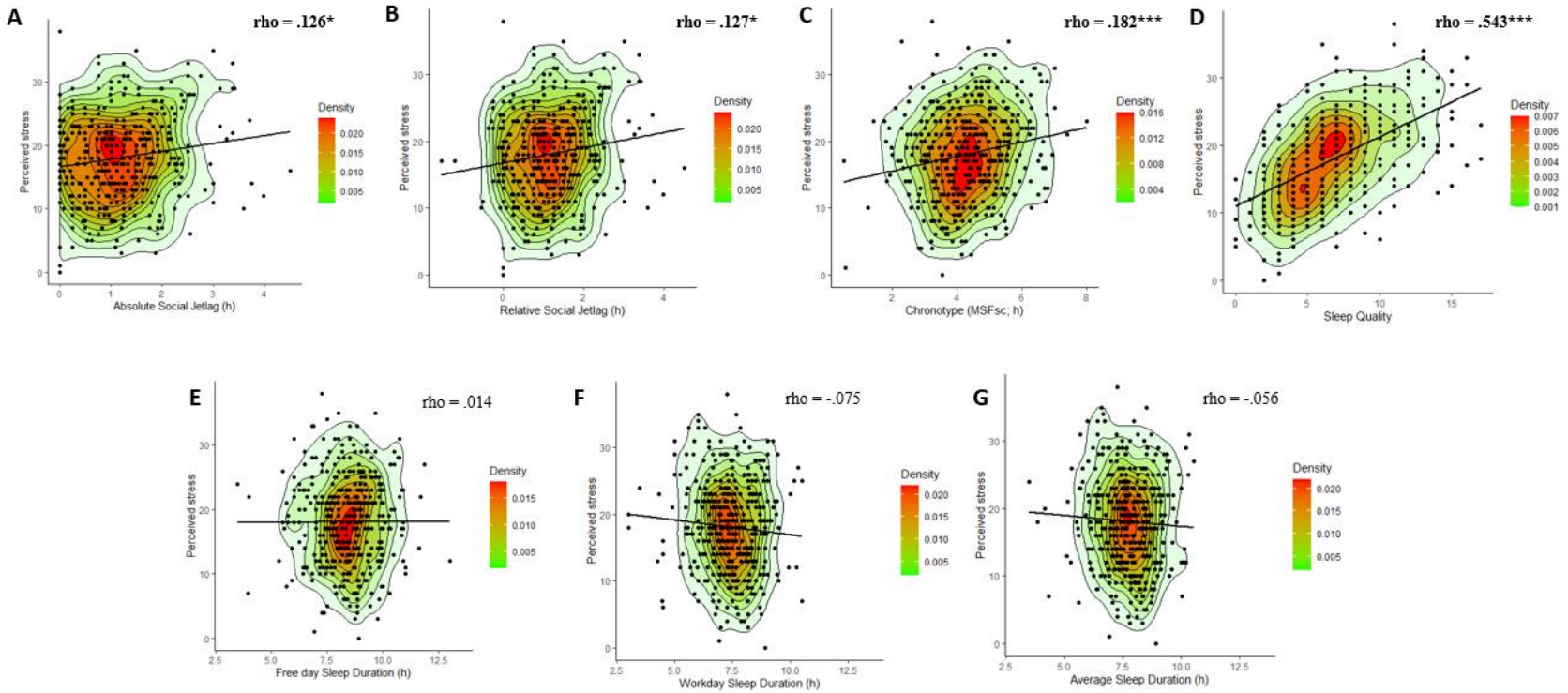


Table 4.3

Associations between sleep and circadian variables and perceived stress in the full sample.

	Relative SJL	Absolute SJL	MSFsc	SDw	SDweek	PSS	PSQI
OA Sample							
Relative SJL	1						
Absolute SJL	**.984*** **	1					
MSFsc	**.515*** **	**.491*** **	1				
SDw	-.019	-.036	**.113***	**1**			
SDweek	**.132****	**.118***	**.153****	**.906*** **	1		
PSS	**.127***	**.126***	**.182*** **	-.075	-.056	1	
PSQI	.046	.058	.082	**-.323*** **	**-.316*** **	**.543*** **	1
Students							
Relative SJL	1						
Absolute SJL	**1*** **	1					
MSFsc	**.509*** **	**.509*** **	1				
SDw	-.191	-.191	.000	1			
SDweek	-.088	-.088	.025	**.961*** **	1		
PSS	.160	.160	.200	.017	.049	1	
PSQI	.190	.190	.199	-.111	-.107	**.568*** **	1
Workers							
Relative SJL	1						
Absolute SJL	**.978*** **	1					
MSFsc	**.515*** **	**.488*** **	1				
SDw	-.013	-.038	.076	**1**			
SDweek	**.146***	**.125***	**.129***	**.891*** **	1		
PSS	.077	.077	.068	**-.137***	-.105	1	
PSQI	.036	.052	.059	**-.397*** **	**-.366*** **	**.533*** **	1
Non-Workers							
Relative SJL	1						
Absolute SJL	**.920*** **	1					
MSFsc	.486	.327	1				
SDw	-.236	-.065	**-.736****	**1**			
SDweek	-.071	.162	**-.582***	**.817*** **	1		
PSS	-.240	-.211	.100	-.209	-.461	1	
PSQI	-.026	-.006	.126	-.210	-.498	**.806*** **	1

Note. All correlations are Spearman's rho due to a number of variables being non-normally distributed.

*** = p < .001, ** = p < .01, * = p < .05. OA sample = overall sample

4.4.6 Predicting Stress with Sleep and Circadian Variables

Hierarchal linear regression was conducted to determine whether absolute SJL was a significant predictor of perceived stress controlling for age, sex, work category (students vs workers), work duration, sleep quality, and chronotype as they showed an association in the correlation analysis. The first step explained 36.0% of the variance in perceived stress $F(_{7, 381}) = 30.64$, $p < .001$. Addition of SJL to the model in step 2 increased the variance explained by .004, which was a non-significant increase $p = .131$. The second step was also significant $F(_{8, 380}) = 27.19$, $p < .001$. Age, sex, and sleep quality were significant predictors for PSS (see Table 4.4). Work category was borderline significant ($\beta = -.093$, $p = .048$).

Table 4.4

Hierarchal regression model predicting perceived stress levels.

	R^2	Adj R^2	B	B	SE	CI 95% (B)
Step 1	.360***	.348***				
Age			**-.12***	**-.07**	**.03**	**-.12 / -.01**
Sex			**.15*** **	**2.59**	**.71**	**1.18 / 3.99**
Work Group			-.09	-1.43	.76	-2.93 / .07
Work Duration			.03	.08	.13	-.18/.34
Sleep Duration			.06	.35	.30	-.24/.94
Chronotype			.06	.37	.27	-.17/.90
Sleep Quality			**.52*** **	**1.01**	**.09**	**.84/1.19**
Step 2	.364***	.351***				
Age			**-.12***	**-.06**	**.03**	**-.12 / -.01**
Sex			**.15*** **	**2.62**	**.71**	**1.22 / 4.02**
Work Group			**-.09***	**-1.52**	**.76**	**-3.019 / -.016**
Work Duration			.02	.08	.13	-.19 / .34
Sleep Duration			.06	.35	.30	-.24 / .93
Chronotype			.03	.18	.30	-.40 / .763
Sleep Quality			**.51*** **	**1.01**	**.09**	**.84 / 1.18**
Absolute SJL			.07	.58	.38	-.17 / 1.34

Note. R^2 = R-squared; Adj R^2 = Adjusted R-squared; β = standardized beta value; B = unstandardized beta value; SE = Standard errors of B; CI 95% (B) = 95% confidence interval for B; N = 400 except for work duration where N = 389; Statistical significance: *p < .05; **p < .01; ***p < .001

4.4.7 Groupwise Analysis of Stress by SJL

We investigated the difference in perceived stress levels between SJL groups using a one-way ANOVA, with Tukey post-hoc analysis. Perceived stress levels were higher in those with > 2 hours SJL (M = 21.00, SE = 0.92) in comparison to those with 1-2 hours SJL (M = 17.71, SE = 0.55) and those with less than 1-hour SJL (M = 17.47, SE = 0.48). Those with less than one-hour SJL and 1-2 hours SJL did not differ significantly; $F(_{2,397}) = 6.39$, p = .002, $\eta^2 = .031$. Age, sleep duration, and MSFsc also differed between groups while PSQI did not (see Table 4.5). The lack of association between SJL and PSQI, and PSQI not differing significantly between SJL groups suggests that the PSQI and SJL effect are not colinear. There was no association between SJL groups and sex (p = .39). Further analysis of the differences between SJL groups were conducted and can be observed in Table 4.5.

Table 4.5

Comparisons of key demographic and sleep-related variables between SJL groups.

	1. Low (<1 hour)	2. Moderate (1-2 hours)	3. High (> 2 hours)	p value
N	189	154	57	
Age	36.57 (0.98)*2,3	31.68 (0.96)*1	29.12 (1.43)*1	<.001
Sex, % F	82.5	76.6	80.7	.391
SDweek	7:32 (0:05)*2	7:56 (0:04)*1	7:34 (0:09)	.004
MSFsc	3:49 (0:05) *2,3	4:34 (0:05) *1,3	5:11 (0:07) *1,2	<.001
PSQI[a]	6.00 (5.00)	6.00 (4.00)	7.00 (5.00)	.095

Note. All data are mean ± SE except for those marked with a superscript a which are reported as median (IQR) due to violations to the assumption of normality. SDweek and MSFsc are reported in hours and minutes.

4.4.8 Analysis of Work-Related Psychosocial Stress

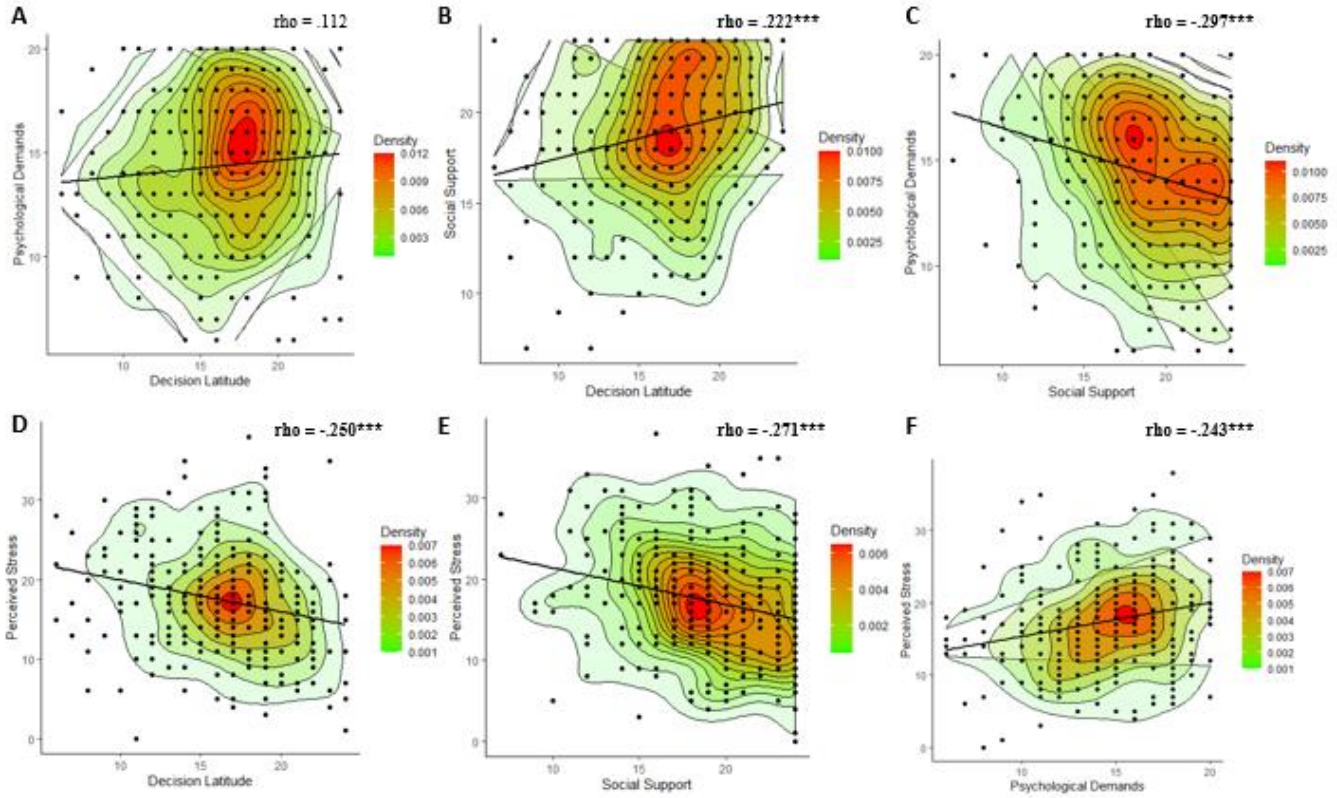
The DCSQ gave three overall scores which are in line with the demand-control-support model of job strain. Since this is a measure work-related psychosocial stress, students, and those outside of the regular workplace were excluded from the analysis of these variables, leaving the sample size at N = 296. All three measures of the demand-control-support model showed acceptable internal consistency reliability.

Psychological demands (*Med* = 15.00, *IQR* = 5.00) had a Cronbach's α of .71, social support (*Med* = 19.00, *IQR* = 5.00) had a Cronbach's α of .84 and decision latitude (*Med* = 17.00, *IQR* = 5.00) had a Cronbach's α of .71.

All of the stress measures showed a small to moderate positive association with each other except psychological demands and decision latitude which demonstrated a weak non-significant association (*rho* = .11, *p* = .054; Figure 4.6). Higher PSS was positively associated with psychological demands and negatively associated with decision latitude and social support (Figure 4.6). In addition to this social support showed a negative association with psychological demands and a positive association with decision latitude (see Table 4.6; Figure 4.6). No significant differences in social support, psychological demands, or decision latitude were observed between males and females (data not shown). Similar to the analysis in the full group, females (*M* = 18.12, *SE* = 0.44) reported higher PSS than males (*M* = 14.80, *SE* = 0.76), *t*(294) = -3.56, *p* < .001, Cohen's *d* = .50.

Figure 4.6

Bivariate associations between the three measures of the job demand-control support model (A-C). The relationship between perceived stress and the three measures of job demand-control support model (D-F). The contour lines are "heat" coloured from green to red which correspond with the plotting density.



Absolute and relative SJL did not show any association with PSS in this subgroup. Absolute SJL also showed no association with psychological demands (*rho* = .01, *p* = .823), social support (*rho* = -.04, *p* = .523), but did display a weak negative association with decision latitude (*rho* = -.14, *p* = .019). Similarly, relative SJL showed no association with psychological demands (*rho* = -.01, *p* = .838), social support (*rho* = -.04, *p* = .488), but did display a weak negative association with decision latitude (*rho* = -.14, *p* = .019). Later chronotype was also associated with lower decision latitude at work (*rho* = -.13, *p* = .022; Figure 4.7). Average weekly sleep duration was inversely associated with psychological demands, and decision latitude. Poorer sleep quality and greater perceived stress showed a moderate association. Poorer sleep quality was also associated with shorter sleep duration, more psychological demands, and less social support. Notably, self-reported workday length, calculated by subtracting work start from work end was positively associated with perceived stress (*rho* = .13, *p* = .025) and psychological demands (*rho* = .16, *p* = .007), but did not show any association with social support (*rho* = -.08, *p* = .204) or decision latitude (*rho* = -.02, *p* = .720). See Table 4.6 for remaining correlation coefficients.

Table 4.6

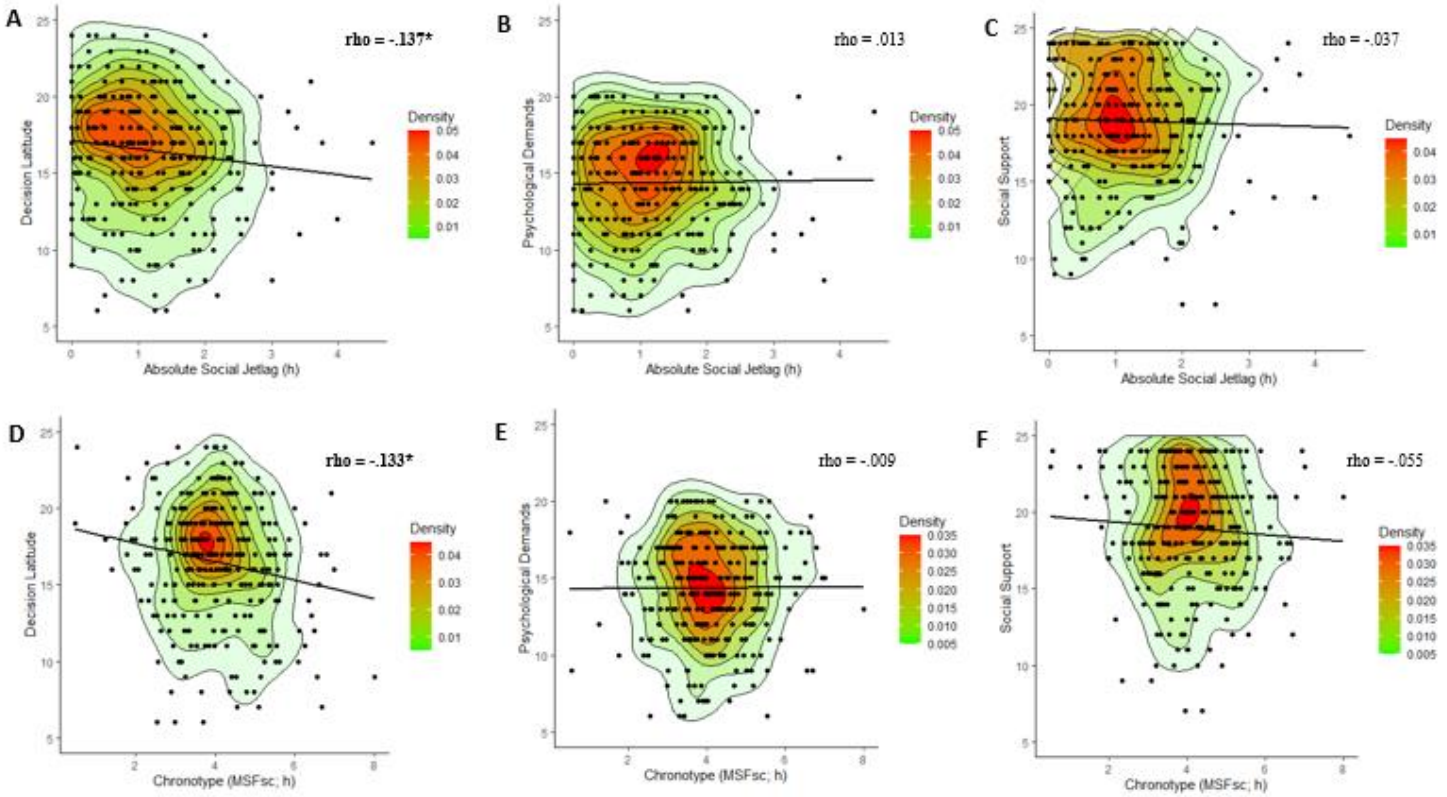
Association between sleep and circadian variables and measures of stress in working participants.

	Relative SJL	**Absolute SJL**	**MSFsc**	**SDweek**	**PSS**	**PD**	**SS**	**DL**	**PSQI**
Relative SJL	1								
Absolute SJL	**.978*** **	1							
MSFsc	**.515*** **	**.488*** **	1						
SDweek	**.146***	**.125***	**.129***	1					
PSS	.077	.077	.068	-.105	1				
PD	-.012	.013	-.009	**-.144***	**.243*** **	1			
SS	-.041	-.037	-.055	.002	**-.271*** **	**-.297*** **	1		
DL	**-.136***	**-.137***	**-.133***	**-.144***	**-.250*** **	.112	**.222*** **	1	
PSQI	.036	.052	.059	**-.366*** **	**.533*** **	**.166****	**-.157****	-.051	1

Note. All correlations are Spearman's rho due to a number of variables being non-normally distributed SJL = social jetlag; SDweek = average weekly sleep duration; PSS = perceived stress; PD = psychological demands; SS = social support; DL = decision latitude. *** = p < .001, ** = p < .01, * = p < .05. All correlations are Spearman's rho.

Figure 4.7

The associations between the measures of the job demand-control-support model and absolute SJL (top row) and MSFsc (bottom row). The contour lines are "heat" coloured from green to red which correspond with the plotting density.



Since decision latitude was the only measure of work-stress associated with SJL in the univariate analysis, a multiple linear regression was conducted to determine if it was a significant predictor beyond other sleep and demographic variables. Earlier chronotype and shorter sleep duration were the only significant predictors of decision latitude, $F(7, 282) = 3.15$, $p = .003$ (see Table 4.7). A similar regression analysis was then conducted with psychological demands and social support as the CVs. The model for psychological demands explained 5.6% of the variance $F(7, 282) = 2.38$, $p = .022$ and the only significant predictor was age ($\beta = .17$, $p = .011$). The model was nonsignificant for social support, $F(7, 282) = 1.89$, $p = .072$.

Table 4.7

Multiple regression model predicting decision latitude.

	R^2	Adj R^2	B	B	SE	CI 95% (B)
Model	.072**	.049**				
Age			-.03	-.01	.02	-.05 / .03
Sex			-.10	-.92	.56	-2.03 / .18
SDweek			**-.17***	**-.61**	**.24**	**-1.07 / -.14**
Workday duration			-.08	-.15	.12	-.38 / .08
MSFsc			**-.14***	**-.47**	**.23**	**-.92 / -.01**
SJL			-.04	-.18	.31	-.79 / .43
PSQI			-.11	-.12	.07	-.26 / .02

Note. R^2 = R-squared; Adj R^2 = Adjusted R-squared; β = standardized beta value; B = unstandardized beta value; SE = Standard errors of B; CI 95% (B) = 95% confidence interval for B; N = 296 for all except workday duration where N = 290; Statistical significance: *p < .05; **p < .01.

Notably for decision latitude, chronotype, and sleep duration were significant predictors while for PSS, sleep quality was a significant predictor. These differential effects are important to note. Also notably sleep duration and sleep quality only showed a small to moderate relationship with each other (*rho* = -.359, $p < .001$) so it is unlikely that sleep duration and sleep quality are colinear.

Nonparametric analysis using Kruskal-Wallis tests indicated that there were no differences between SJL groups for any of the three measures on work stress in this subgroup. For social support low (*Med* = 19.00, *IQR* = 5.00), moderate (*Med* = 19.00, *IQR* = 5.00) and high SJL (*Med* = 21.00, *IQR* = 6.00) did not differ significantly p = .965. For psychological demands low (*Med* = 15.00, *IQR* = 5.00), moderate (*Med* = 15.00, *IQR* = 4.00) and high SJL (*Med* = 14.00, *IQR* = 5.00) did not differ significantly, p = .362. For decision latitude, low (*Med* = 17.50, *IQR* = 4.00), moderate (*Med* = 17.00, *IQR* = 5.00) and high SJL (*Med* = 16.00, *IQR* = 7.00) did not differ significantly, p = .063. Perceived stress differed between groups in this subgroup similar to the full sample.

4.4.9 Job Strain and Measures of Sleep Timing

An estimate of job strain was calculated from the scores participants reported for psychological demands and decision latitude. Psychological demands was divided into high and low demands based on a median split (i.e., ≥ 15 indicated high demands while < 15 indicated low demands). Decision latitude was also divided into high and low job control based on a median split (i.e., ≥ 17 was an indicator of high control and < 17 indicated low control). These two categorical variables were then used to categorise participants into one of four groups according to the demand control model (Karasek, 1979). There was a low strain group (low demands, high control), a high strain group (high demands, low control), an active group (high demands, high control) and a passive group (low demands, low control). Based on the self-reported job demands and control, 68 (23%) were categorised into the low strain group, 76 (25.7%) were categorised into the passive group, 97 (32.8%) into the active group and 55 (18.6%) into the high strain group. All descriptive details for each group can be observed in Table 4.8.

Table 4.8

Descriptive statistics of the participants by job strain group.

	All	Low strain (n = 68)	Passive job (n = 76)	Active job (n = 97)	High strain (n = 55)	p
Characteristics	**Med(IQR)/N (%)**	**Med(IQR)/N (%)**	**Med(IQR)/N (%)**	**Med(IQR)/N (%)**	**Med(IQR)/N (%)**	
Age	32.00 (21)	34.00 (23)	27.50 (18)	36.00 (18)	32.00 (21)	.005
Gender						
Male	65 (22)	19 (29.2)	16 (24.6)	22 (33.8)	8 (12.3)	.355
Female	231 (78)	49 (21.2)	60 (26.0)	75 (32.5)	47 (20.3)	
Occupational status						
Professional	173 (58.4)	44 (23.6)	28 (16.2)	70 (40.5)	31 (17.9)	.006
Assistant Professional	24 (8.1)	4 (16.7)	8 (33.3)	7 (29.2)	5 (20.8)	
Administration	36 (12.2)	8 (22.2)	12 (33.3)	10 (27.8)	6 (16.7)	
Sales & Services	50 (16.9)	9 (18.0)	21 (42.0)	9 (18.0)	11 (22.0)	
Manual Labour	13 (4.4)	3 (23.1)	7 (53.8)	1 (7.7)	2 (15.4)	
Contract						
Part-time	71 (24.0)	17 (23.9)	28 (29.4)	13 (18.3)	13 (18.3)	.005
Full-time	225 (76.0)	51 (22.7)	48 (21.3)	84 (37.3)	42 (18.7)	

Note. For age the only significant differences were between those with a passive job and an active job.

The measures of sleep duration (weekday, weekend day and average) did not vary too much from the normal distribution based on visual inspection and inspection of the skewness and kurtosis values. Therefore, parametric analysis were conducted. Workday and free-day sleep duration did not differ significantly between groups (see Table 4.9). Additional variables from workdays (bedtime, sleep onset, midsleep and sleep end) all had a leptokurtic distribution and so differences between groups were analysed using non-parametric statistics (see Table 4.9). Additional differences between free day variables and SJL are also included in Table 4.9. The only significant difference observed was that those with a passive job had a longer average sleep duration than those with an active job.

Table 4.9

Comparison of sleep timing variables between job strain groups.

	All	Low strain (n = 68)	Passive job (n = 76)	Active job (n = 97)	High strain (n = 55)	P
Characteristics	**M(SD)/N (%)**	**M(SE)/N (%)**	**M(SE)/N (%)**	**M(SE)/N (%)**	**M(SE)/N (%)**	
BTw[a]	23.00 (1.50)	23.00 (1.00)	23.00 (1.38)	23.00 (1.50)	23.00 (1.50)	.529
SOw[a]	23.58 (1.19)	23.33 (1.15)	23.60 (1.15)	23.67 (1.17)	23.75 (1.17)	.385
SEw[a]	7.00 (1.00)	6.79 (1.44)	7.00 (1.96)	7.00 (1.00)	7.00 (1.25)	.345
MSW[a]	3.33 (1.03)	3.25 (1.03)	3.33 (1.24)	3.29 (0.92)	3.38 (1.21)	.282
SDw	7.28 (1.15)	7.25 (0.13)	7.49 (0.13)	7.12 (0.11)	7.32 (0.18)	.206
SDf	8.38 (1.34)	8.33 (0.15)	8.68 (0.15)	8.14 (0.12)	8.49 (0.23)	.062
BTf[a]	23.50 (1.00)	23.00 (1.00)	23.25 (1.38)	23.50 (1.00)	23.50 (1.50)	.519
SOf[a]	24.17 (1.53)	24.08 (1.13)	24.25 (1.64)	24.50 (1.25)	24.50 (1.83)	.384
SEf[a]	9.00 (1.50)	8.50 (2.38)	9.00 (2.00)	8.50 (2.00)	9.00 (2.00)	.049
MSF	4.48 (1.20)	4.20 (0.13)	4.69 (0.13)	4.41 (0.12)	4.65 (0.17)	.056
MSFsc	4.07 (1.13)	3.81 (0.12)	4.28 (0.13)	4.01 (0.11)	4.20 (0.17)	.062
Relative SJL[a]	1.00 (1.17)	0.85 (1.11)	1.25 (1.08)	1.00 (1.13)	1.25 (1.17)	.176
Absolute SJL[a]	1.04 (1.17)	.85 (1.11)	1.25 (1.08)	1.00 (1.08)	1.25 (1.13)	.164
PSQI[a]	6.00 (5.00)	5.00 (4.00)	6.00 (5.00)	7.00 (4.50)	7.00 (5.00)	.027
Average SD	7.64 (1.09)	7.59 (0.12)	7.92 (0.12)	7.41 (0.10)	7.72 (0.17)	.018

Note. For average sleep duration the only significant differences were between those with a passive job and an active job. For PSQI the only significant difference after Bonferroni correction for multiple comparisons was between those with low and high strain. SDw = sleep duration on workdays, SDf = sleep duration on free days, SD = sleep duration, BTw = bedtime workdays, SOw = sleep onset workdays, SEw = sleep end workdays, MSW = midsleep workdays. Superscript [a] indicates a violation of the assumption of normality and data here is median (IQR). All variables except PSQI are presented in decimalised time.

4.4.10 Acknowledging the Potential Impact of the Pandemic

The COVID-19 pandemic occurred in the middle of data collection. Recruitment was therefore stopped for a number of months (March 2020 – September 2020) while people were learning to live with COVID-19. Recruitment recommenced in September 2020 and 43% of the sample were recruited between September 2020 and December 2020. No significant differences in SJL, MSFsc, average sleep duration or sleep quality were observed between participants who participated before the onset of the pandemic and after the onset of the pandemic. Commute to work/college did decrease significantly. Perceived stress did not differ between groups. In terms of work-stress among those in full-time employment social support and psychological demands did not differ between those recruited pre and post COVID-19 onset. Participants reported slightly lower decision latitude after the onset of the pandemic (Table 4.10).

Table 4.10

A comparison of some of the main variables that were collected from one group of participants before the COVID-19 pandemic and another group of participants that were collected after the pandemic.

	Pre-Covid Onset	**Post-Covid Onset**	**p value**
N	**228**	**172**	
Absolute SJL (hours:mins)	1:16 (0:03)	1:07 (0:04)	.073
Relative SJL (hours:mins)	1:14 (0:04)	1:04 (0:49)	.057
MSFsc (hours:mins)	4:13 (0:05)	4:25 (0:05)	.080
SDweek (hours:mins)	7:39 (0:04)	7:47 (0:05)	.179
Commute to work (mins)	28.53 (1.77)	18.82 (2.17)	<.001
PSS	18.36 (0.45)	17.69 (0.52)	.331
PSQI[a]	7.00 (4.00)	6.00 (6.00)	.066
	187	**109**	
Social support[a]	19.00 (4.00)	20.00 (6.00)	.223
Decision latitude[a]	17.00 (4.00)	16.00 (6.50)	.014
Psychological demands[a]	14.00 (5.00)	15.00 (4.00)	.075

Note. Data are mean ± SE, except when marked by a superscript a. The data here are median ± interquartile range. Social support, decision latitude and psychological demands were investigated only in workers. Other variables were investigated in the full sample.

4.5 Discussion

SJL was prevalent in this group. This equated to 47.3% of the sample displaying less than one-hour SJL, 38.5% of the sample displaying 1-2 hours SJL and 14.2% of the sample displaying more than 2 hours SJL. This is slightly higher than a recent Japanese study investigating SJL and stress reactions (Adachi et al., 2021). This study reported that just over half of the sample displayed less than one-hour SJL (55.8), 35.4% displayed 1-2 hours and 8.9% displayed more than 2 hours. SJL has been reported as higher in European countries, so this is not surprising. For example, Roenneberg et al. (2013) reported that 69% of participants had SJL of at least 1 hour. Interestingly, in our subsample of people in employment SJL was slightly lower than the cohort as a whole. Of these workers just under half had less than 1 hour (49.3%), 37.5% had 1-2 hours and 13.2% had greater than 2 hours. This was more comparable with Adachi and colleagues (2021). The workers having less SJL than the sample as a whole needs to be understood in the context of the people being excluded were undergraduate students. University students are likely to have a very late chronotype and large amounts of SJL due to their university schedule (Roenneberg et al., 2013).

Research on any association between SJL and perceived stress is scarce. Previous research on the association between SJL and depressive symptoms coupled with the fact that SJL is a physiological stressor led us to hypothesise that there may be a positive association between SJL and greater perceived stress levels. We hypothesised this despite Jokubauskas et al. (2019) identifying no bivariate association between SJL and perceived stress in students. In the bivariate analysis higher levels of perceived stress was weakly associated with more absolute SJL, relative SJL, and later chronotype. This was in contrast to the lack of an association found in Jokubauskas et al. (2019) and in line with our prediction. However, SJL was not a significant predictor of perceived stress levels when we controlled for other covariates including age, sex, chronotype, and sleep quality. The only significant predictors were poorer sleep quality, younger age and being female.

Consistent with our findings, poorer sleep quality has been reported to be associated with higher perceived stress in some previous research (Zhao et al., 2021; Charles et al., 2011). A recent study in China during the COVID-19 pandemic demonstrated a relationship between greater perceived stress and poorer sleep quality

(Zhao et al., 2021). Other previous research found an association between poorer sleep quality and higher perceived stress, but this only reached significance in males. It needs to be considered that stress may lead to poor sleep quality and that the reverse could also be true, poorer quality sleep could lead to higher perceptions of stress.

Contrastingly, SJL did not show a clear association with perceived stress levels despite SJL being prevalent in our sample. No previous studies to the best of our knowledge have set out specifically to describe the association between SJL and perceived stress in a group of students and workers. However, in some previous research, greater SJL has been associated with greater likelihood of experiencing depressive symptoms, linking it to stress-related symptoms (Islam et al., 2020; Levandovski et al., 2011). However, previous research has also failed to find an association between SJL and depressive symptoms (de Souza & Hidalgo, 2014; Knapen et al., 2018). Chronotype also showed no association with perceived stress levels in the multivariate analysis suggesting that an individual's underlying circadian prevalence does not put someone at a greater risk for stress. Research by Jokubauskas et al. (2019) also did not find any association between chronotype and perceived stress. Those who were younger, and female also displayed higher perceived stress levels. The finding that females experience more perceived stress parallels some previous research. Higher levels of perceived stress have previously been reported in college females in comparison to males (Graves et al., 2021), and females starting a new job after a period of unemployment than males in the same situation (Costa et al., 2021). Further, university life can place many competing demands on the typical young adult, and this may explain why younger age was associated with higher perceived stress.

The second objective of this study was to assess the association between SJL and the components of the job demand-control-support model (psychological demands, decision latitude and social support). This model was chosen as these factors are commonly used to investigate psychosocial aspects of the workplace (de Aguiar et al., 2010). Bivariate analysis identified a weak association between SJL and only the decision latitude component of this model. Greater decision latitude can generally be conceptualised as a positive aspect of work as it has previously been shown to have a protective effect against depression (Theorell et al., 2015). However, multivariate linear regression revealed that as chronotype gets later and as sleep duration gets longer decision latitude decreases. SJL was not a significant predictor here. The only

significant predictor of psychological demands was younger age and there were no significant predictors of social support. It is possible that those with an earlier chronotype and those with a shorter sleep duration have more control over their work. The lack of a clear association between SJL and job stress is surprising as a recent study found an association between SJL with job stress, while chronotype was not a significant predictor (Takaesu et al., 2021). This study did use a different measure of job stress.

Furthermore, since decision latitude is only one aspect of the job demand-support-control model it is hard to understand what role increased decision latitude will have on how the participants experience their job. For example, high control with low demands leads to low job strain but high demands with high strain leads to an active job (Myllyntausta et al., 2021). Both of these job conceptualisations may have a different effect.

For this reason, the measure of psychological demands and decision latitude were used to make a categorical variable of high strain, low strain, active job, and passive job and comparisons between groups were conducted. Those with high strain reported poorer sleep quality than those with low job strain which is similar to previous research (De Lange et al., 2009; Leitaru et al., 2019). Like previous research no differences in sleep duration were found between those with high and low strain (Karhula et al., 2013). Those with passive jobs did have a longer average sleep duration than those with active jobs. Furthermore, sleep duration on work and free days did not differ between job strain groups. This is partly in line with previous research by Myllyntausta et al. (2021) who found no differences between job-strain groups for workday sleep duration. Myllyntausta et al. (2021) did however find that those with high strain had a longer free-day sleep duration than those with low strain jobs. This sample was mainly composed of an older working population closer to retirement which may explain some of the differences. Myllyntausta et al. (2021) also used some questions from the JCQ while our study utilised the DCSQ.

Chronotype and SJL also did not differ between job-strain groups. These findings add to the initial regression analysis to suggest that SJL does not have any impact on job strain or support as measured by the DCSQ in this group of mostly professional workers. The relationships between the stress subscales are important to

consider as the lack of an association between psychological demands and decision latitude suggests psychological demands and the associated responsibility were not influenced by skill level or authority in this sample (Karasek et al., 1998).

4.5.1 Strengths and Limitations

This research has several strengths. The MCTQ, PSQI and PSS are the gold standard scales for assessing sleep timing, sleep quality, and global stress, respectively. The DCSQ also provides a measure of the three core components of work-related stress. While the use of the MCTQ, PSQI, PSS and DCSQ is a strength, it may also be viewed as a limitation due to their self-report nature. Objective measures of sleep timing, specifically SJL, would be optimal. Further, due to its cross-sectional nature causal relationships cannot be determined. Notably, while all items for decision latitude, psychological demands, and social support showed acceptable reliability and provide a good measure of these three components of the demand-control-support model, it should be noted that phrasing of questions varied slightly from a recent validation study (Mauss et al., 2018). While a sample size calculator stated that the sample size was sufficient for study 1, convenience sampling resulted in a much larger proportion of females than males, a more balanced sample would have been preferrable in order to ensure generalisability. Also, for the association with work stress the sample size calculator suggested we had enough to identify a medium effect size; however, a larger sample would be optimal to identify any potential small effects.

One unavoidable limitation to this study was the COVID-19 pandemic which occurred mid data collection. To counteract implications of this, no data was collected from March 2020 until September 2020 due to the unexpected nature of COVID-19 and the new experiences that individuals were going through. However, 43% of our sample for study 1 was recruited from September – December 2020 and there were unavoidable changes in people's lives in this time that may have increased stress levels such as working from home or decreased stress levels such as decreased commute time. However, we argue that by the time we recommenced recruitment people had adjusted to many of these changes. To determine the effect that this had on our primary variables we compared the group that were recruited before and after the onset of the COVID-19 pandemic for our primary variables. SJL decreased slightly, however there was no significant change. This was not unexpected due to reduced commute times

for example and recent research has actually identified larger differences (Raman & Coogan, 2021). There were also no significant differences between chronotype, sleep quality or average sleep duration across the week. Perceived stress did not differ between participants. Decision latitude was slightly lower after the onset of the pandemic, but social support and psychological demands were not significantly different between groups, so it is unlikely that this had a major effect on our findings.

4.6 Study 2: *Association between Social Jetlag and Stress Reactivity in the Laboratory.*

4.7 Methods

4.7.1 Participants

Fifty-seven students (males = 22, females = 35) were recruited from Maynooth University from September 2019, until March 2020. Recruitment was planned until the end of June 2020 but was stopped due to the onset of the COVID-19 pandemic. Some participants were recruited from the psychology department participant pool while others were recruited from announcements and flyers at Maynooth University. Potential participants were screened before participating and those who were clinically obese or underweight (body mass index above 30 kg/m^2 or below 18.5 kg/m^2, respectively), a smoker, using any hormonal contraceptives or suffering from any cardiovascular conditions were excluded due to the possible confounding effects on physiological stress reactivity measures. Despite the screening five were excluded after checking BMI (2 obese and 3 underweight) leaving the usable sample size at 52 (males = 21, females = 31). Participants could not eat, drink anything except water, chew gum, brush teeth or use mouthwash for 1h prior to coming in and they also could not participate in vigorous activity or consume caffeine for 3 h prior to participation. All participants were given a detailed information sheet, given the opportunity to ask any questions and provided informed consent. This study was approved by the Biological Research Ethics Sub-Committee at Maynooth University and was conducted in accordance with the Declaration of Helsinki.

4.7.2 Measures

Heart rate (BPM) and blood pressure (BP), both systolic and diastolic, were measured non-invasively using the dinamap carescape vital signs monitor. This involved putting the blood pressure monitor on the upper arm of the participant's non-dominant arm. The cuff was fitted to each participant upon arrival and a practice measurement was taken in order to familiarize participants with the procedure. It took approximately 30 seconds to take a reading of BP and BPM. The MCTQ was used to measure participants' chronotype and SJL, and the PSQI was used to provide a measure of overall sleep quality. These surveys are described in detail in the methods for chapter 2. Notably, for the purpose of this experiment since students participated,

they were told to take a college day with college work/lectures as a typical "workday" and a weekend day (without any part-time work) as a "free day". Poor sleep quality was classed as a global PSQI score greater than 6 as researchers have suggested that a cut off of 5 may be overly sensitive especially in a student population (Manzar et al., 2016).

4.7.3 Procedure

The socially evaluative cold-pressor task (SECPT) was utilised in this experiment, which combines the physiological stressor of ice-cold water with the socially evaluative component of being video recorded and watched by the researcher throughout. The experiment was conducted in a laboratory in the Psychology Department at Maynooth University between 13:30 and 15:30 h to control for the diurnal cycle in physiological markers of stress. Prior to the experiment beginning, the participants were randomly assigned to one of two groups. Group 1 was the experimental group / ice-water group (n = 15 females, 13 males) while group 2 was the control group / room-temperature water group (n = 16 females, 8 males). All parameters other than water temperature were the same for both groups. The experimenter (female) wore a white lab coat and remained constant for the experiment. The experimenter acted in a reserved manner (without being impolite) from the beginning experiment up until the task had ended. This was to help ensure that the socially evaluative aspect of the experiment would work; otherwise, it is possible that if the researcher was too friendly with participants, they were less likely to find the presence of the researcher stressful (Schwabe et al., 2018).

After consent was obtained, the participants' demographic details were recorded, and height and weight were assessed in light clothing to determine accurate BMI measurements. The participants were then shown the blood pressure machine and a practice measurement was obtained using an upper arm cuff on the non-dominant arm. The participants were asked to relax for a total duration of 15 minutes in order to adapt to the experimental setting. After the relaxation period baseline measurements were taken for 5 minutes. Three BP and HR measurements were obtained. The participants were then asked to rate their current sleepiness levels on the Karolinska sleepiness scale (KSS) from 1 (extremely alert) to 10 (extremely sleepy, can't keep awake; Gillberg et al., 1994). This was to ensure that any reactions were

not simply due to increased alertness or sleepiness. After this the participants in both groups were given written instructions for the task that falsely informed them that they would be videotaped while they immersed their dominant hand in the water and that their facial expressions would be analysed. This as well as being observed by the researcher for the duration were the socially evaluative aspects of the experiment.

These instructions stated that individuals had to maintain eye contact with the camera and would be told when they could remove their hand from the water (see Appendix D). The participants were sat in the laboratory with the blood pressure machine on their non-dominant side. A camera was placed in front of them, and the screen was flipped so that they were staring at themselves. Next an insulated box with water was placed on their dominant side. For group one this contained ice water (0–2 °C) and for group 2 this contained room temperature water (20–22 °C). The experimenter watched the participants all the time and stood in the middle of the blood pressure machine and the camera forming an equilateral triangle to be visible in the participants' peripheral vision. The experimenter always held a clipboard to take notes during the task. No participant in the control group removed their hand before being asked to do so. In the experimental condition, participants kept their hand in the water for an average of 165 seconds and notably only 4 participants removed their hand before being asked to do so. Those participants who kept their hand in the water for 3 minutes were instructed at that point to remove their hand. Blood pressure measurements were taken at two points during the task: immediately after hand submersion, and 1 minute after hand submersion. Immediately after the participants removed their hand from the water, they were asked to rate how unpleasant, stressful, and painful they found the task on an 11-point scale ranging (in 10-point increments) from 0 ("not at all") to 100 ("very much") similar to the study conducted by Schwabe et al. (2008). Participants were taken through the two surveys discussed above and were then given an emotionally neutral magazine to read for 15 minutes and asked to relax. After this resting period BP and BPM was measured for another 5 minutes, this involved taking three measurements, same as baseline measurement.

4.7.4 Data Analysis

All analysis was conducted using Microsoft excel and IBM SPSS 26.0. Three measurements of BP and BPM were taken at baseline and the average was used. The

physiological reaction was taken as the average BP and BPM immediately following submersion and one minute after submersion. If the participant removed their hand before the second measurement (N = 3) their first measurement alone was used. Three measurements were taken again during the resting period and the average of the three resting measures after the 15-minute rest period were used.

Depending on the normality of the data either parametric or non-parametric analysis were conducted. Independent samples t-tests or Mann-Whitney U tests were used to compare demographic and sleep-related variables between groups. Mann Whitney U tests were also used to compare subjective ratings between groups. To determine task performance and whether the procedure was working as expected, three 2x3 mixed ANOVAs were conducted with group (ice cold or control) as the between groups factor and time (baseline, during task, and resting) as the within groups factor, to compare differences for systolic BP, diastolic BP, and BPM. Three 2x2x3 ANOVAs were then conducted which built on the above analysis and had an additional between groups variable (high and low SJL). For associations between variables if variables were normally distributed Pearson's r was used; however, if the data was non-normal Spearman's rho was used.

4.8 Results

4.8.1 Descriptives

A total of 52 individuals were analysed. Of these participants 28 participated in the experimental condition (cold water) and 24 participated in the control condition (room temperature water). Breakdown of the key demographic variables in both groups can be observed in Table 4.11. Groups were well matched in terms of age and gender. Mean BMI was in the normal range (M = 23.37, SD = 2.61), ranging from 18.53 to 29.98 and was normally distributed (Kolmogorov- Smirnov sig. = .149). BMI did not differ significantly between groups.

PSQI and average weekly sleep duration were non-normally distributed so a Mann Whitney U test was used to determine any significant differences between the control and experimental group. Median PSQI of the group was 6 (IQR = 4) and this did not differ between groups (U = 326.0, z = -.185, p = .853). Individuals slept for an average 7 hours and 45 minutes per night (SD = 1:07) and this did not differ between groups (U = 304.5, z = -.578, p = .563). Mean relative SJL was 1:28 (SD = 1:01) and mean absolute SJL was slightly higher (M = 1:34, SD = 0:51). Relative and absolute SJL were normally distributed (Kolmogorov-Smirnov sig. = .063, .200, respectively). Independent samples t-tests revealed that neither version of SJL differed between groups. Mean chronotype was shortly after 5 am (M = 5:08, SD = 1:25) and did not differ between groups. Average coffee consumption per week was 8.52 cups (SD = 10.21), median value was 4 and this ranged from 0-42. This did not differ between groups (U = 305.50, z = -.573, p = .567). Notably this also did not differ between those with high (>1 hour) and low SJL (≤ 1 hour; p = .975). This all demonstrates that those in the experimental and control group were well matched on all demographic, and sleep variables (see Table 4.11).

Table 4.11

Demographic variables in the experimental (ice-water) and control group (room temperature water).

	Experimental	Control	p-value
N	28	24	
Age	21.82 (0.96)	23.79 (1.57)	.276
%, female	53.6	66.7	.337
BMI	23.16 (0.48)	23.62 (0.56)	.535
PSQI[a]	6.50 (5.00)	6.00 (2.00)	.853
Absolute SJL	1:40 (0:10)	1:26 (0:10)	.304
Relative SJL	1:29 (0:13)	1:26 (0:10)	.850
SDweek	7:40 (0:12)	7:50 (0:14)	.598
MSFsc	5:07 (0:16)	5:08 (0:17)	.500
KSS[a]	4.00 (4.00)	4.00 (4.00)	.889
Weekly coffee consumption[a]	4.00 (14.00)	5.50 (14.00)	.567

Note. Superscript a denotes non-normally distributed variables and data here are median ± interquartile range. All other data are mean ± standard error or percentage for categorical variables. Absolute/ Relative SJL, SDweek and MSFsc reported in h:mm.

There were three indicators of physiological stress responses: systolic BP, diastolic BP, and BPM. Baseline systolic BP and BPM were normally distributed (Kolmogorov- Smirnov sig. = .200 for both). Baseline diastolic BP had a Kolmogorov-Smirnov significance statistic was slightly under .05 (p = .015); however, upon visual inspection there were no major outliers, and skewness and kurtosis were both below .51. Therefore, we proceeded with parametric statistics for these three variables. None of the sleep and circadian measures recorded were associated with any of the baseline physiological markers (see Table 4.12).

Table 4.12

The association between sleep and circadian variables and baseline physiological stress markers.

	Systolic BP	Diastolic BP	BPM
Absolute SJL	-.180	-.072	-.053
Relative SJL	-.107	-.003	-.027
SDweek	-.182	-.224	.110
SDF	-.064	-.059	.160
SDW	-.215	-.250	.102
MSFsc	-.216	-.147	-.138
MSW	-.114	-.102	-.110
PSQI	.046	.109	.051

Note. All correlations are Pearson's r, except those with PSQI where Spearman's rho was used due to PSQI violating the assumption of normality, no associations reached significance.

4.8.2 Task Performance

The three physiological markers of stress were assessed at three time points: baseline, during submersion and when resting. Three measurements of each marker were taken at baseline and resting, and the average was used (T1 and T3 respectively). Two measurements of the three physiological markers were taken during the task; the first immediately following hand submersion and a second one-minute following submersion. An average of these two time-points was taken as the measure at (T2 during submersion). Three participants removed their hands at or before 60 seconds so there was no measurement recorded for one minute following submersion here and the measurement from immediately following submersion was used.

A mixed between-within ANOVA revealed a significant interaction between condition and time point for systolic BP, Wilks' Lambda = .448, $F(_{2,49}) = 30.20$, $p < .001$, $\eta_p^2 = .552$. For this reason, we split the file by condition and carried out two one-way repeated measures ANOVAs, one in each group. Time was significant in the experimental condition as expected, Wilks' Lambda = .099, $F(_{2, 26}) = 118.72$, $p < .001$, $\eta^2 = .901$, with post-hoc analysis revealing an increase in systolic BP from baseline to T2 and then a decrease again at T3. T1 and T3 did not differ significantly from each other here. However, surprisingly systolic BP also increased but to a smaller degree during the task in the control condition, Wilks' Lambda = .652, $F(_{2,22}) = 5.91$, $p = .009$,

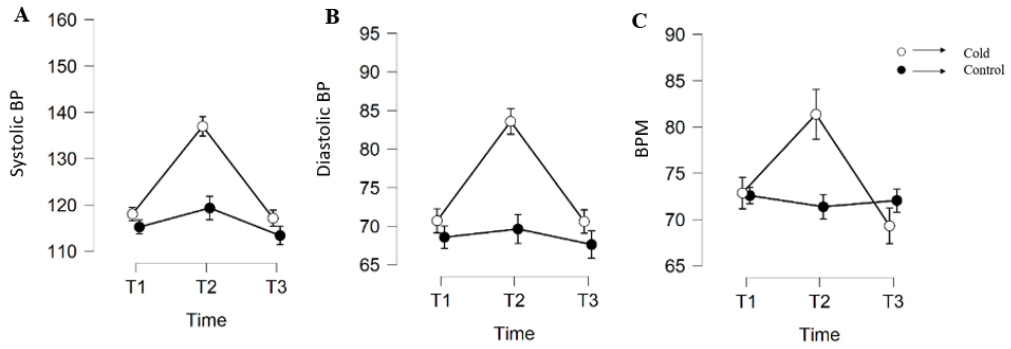
η^2= .348. Systolic BP rose from T1 to T2 and then decreased again. The differences between systolic BP at the three time points between controls and those in the experimental group were also assessed. There was no significant difference at baseline, at time 2 the experimental group had a significantly higher systolic BP and at time 3 after rest there was no significant difference (see Figure 4.8A).

The mixed between-within ANOVA for diastolic BP revealed a significant interaction between condition and time point, Wilks' Lambda = .452, $F(2, 49) = 29.72$, $p < .001$, η_p^2= .548. Similar to systolic BP, the file was split by the group and two one-way repeated measures ANOVAs were conducted. There was a significant effect of time in the experimental group, Wilks' Lambda = .136, $F(2,26) = 82.88$, $p < .001$, η^2= .864. Post-hoc analysis revealed that diastolic BP increased from baseline to T2 and then decreased again to resting. Baseline and resting did not differ in this group. There was no significant effect of time in controls, Wilks Lambda = .909, $F(2,22) = 1.10$, p = .349 (see Figure 4.8B; Table 4.13). The difference in diastolic BP at each time point was also assessed. Diastolic BP was similar in both groups at baseline. During submersion, the experimental group had a significantly higher diastolic BP and diastolic BP fell during the resting period and was similar in both groups (see Figure 4.8B).

The mixed between-within ANOVA for BPM revealed a significant interaction between condition and time point, Wilks' Lambda = .568, $F(2, 49) = 18.61$, $p < .001$, η_p^2 = .432. Similar to both measures of BP, the file was split by group and two one-way repeated measures ANOVAs were conducted. In the cold condition there was a significant effect of time, Wilks' Lambda = .352, $F(2,26) = 23.92$, $p < .001$, η^2= .648. Post-hoc analysis revealed that BPM increased from baseline to T2 and then decreased again when resting. Interestingly, when resting individuals had a lower BPM on average than at baseline. There was no significant effect of time in the control group, Wilks' Lambda = .883, $F(2,22) = 1.45$, p = .256, η^2= .117. The difference in BPM at each time point was also assessed. Baseline BPM was similar in both groups. During submersion those in the experimental group had a significantly higher BPM. Resting BPM was also similar in both groups (see Figure 4.8C). This all suggests that the experiment ran correctly; however, the increase in systolic BP from T1 to T2 was unexpected. Individuals in the experimental condition displayed increased BP and BPM during submission in comparison to baseline and resting measures.

Figure 4.8

Systolic BP, diastolic BP and beats per minute (BPM) during the task.



Note. T1 (time point 1) refers to average at baseline, T2 (time point 2) is during submersion (average of upon submersion and one minute following submersion) and T3 (time point 3) is the average after resting. Figure A shows change in systolic BP for both controls and those in the experimental group over the three time points. Figure B shows the same but for diastolic BP and Figure C shows this for BPM. In the experimental group all values changed from baseline to T2. The control condition values did not change significantly over the task for diastolic BP or BPM. There was a very slight change from T1 to T2 for systolic BP. Controls are indicated by the closed circles and the experimental group are indicated by the open circles on the figure as indicated by the figure legend. All figures include 95% error bars.

Another measure we assessed was the actual change in BP and BPM between baseline and submersion and between submersion and resting. This was assessed using an independent samples t-test where the change value was compared between groups. As expected, those in the ice-water condition displayed greater changes from T1 to T2 in systolic BP (M = 18.44, SE = 1.32), diastolic BP (M = 12.89, SE = 1.21) and BPM (M = 8.14, SE = 1.71) than controls did for systolic BP (M = 4.09, SE = 1.44), diastolic BP (M = 1.06, SE = 1.12) and BPM (M = -1.20, SE = 0.74), all $p < .001$. Similar findings occurred for the change between T2 and T3. Those in the ice-water group showed larger changes for systolic BP (M = 19.11, SE = 1.50), diastolic BP (M = 12.97, SE = 1.22) and BPM (M = 11.38, SE = 1.84) than controls did for systolic BP (M = 5.94, SE = 1.69), diastolic BP (M = 2.01, SE = 1.32) or BPM (M = -0.67, SE = 0.95), all $p < .001$.

In order to determine if alertness as measured by the KSS potentially played a role, the association between the KSS score and all measures of BP and BPM were

assessed in the full sample. Only baseline systolic BP showed a significant, negative association with KSS, suggesting those with higher baseline systolic BP were more alert (*rho* = -.353, *p* = .010). This remained significant in the control condition (*rho* = -.453, *p* = .026) but not the cold condition (*rho* = -.298, *p* = .123). No other associations were significant in either group.

In terms of the subjective ratings, those in the experimental group reported the experience to be more stressful, unpleasant, and painful than controls. These are also in the direction that would be expected (see Table 4.13).

Table 4.13

Task performance in both groups.

Group:	**Experimental**	**Controls**	**p-value**
Systolic BP	N = 28	N = 24	
T1	118.05 (2.12)	115.26 (2.17)	*.363*
T2	137.00 (2.39)	119.35 (3.00)	*<.001*
T3	117.15 (2.23)	113.42 (2.12)	*.234*
Diastolic BP			
T1	70.73 (1.56)	68.58 (1.19)	*.284*
T2	83.59 (1.65)	69.65 (1.44)	*<.001*
T3	70.62 (1.65)	67.64 (1.33)	*.176*
BPM			
T1	72.88 (2.19)	72.60 (2.42)	*.931*
T2	81.38 (2.62)	71.40 (2.16)	*.006*
T3	69.33 (1.86)	72.07 (2.23)	*.346*
Self-rating			
Unpleasant[a]	80 (18)	10 (38)	*<.001*
Stressful[a]	55 (30)	10 (30)	*<.001*
Painful[a]	70 (20)	00 (18)	*<.001*

Note. T1= baseline, T2 = average during submersion, T3 = resting. BP = blood pressure, BPM = beats per minute. Superscript a indicates non-normally distributed variables and data reported are median and interquartile range to reflect this. All other data are means and standard error.

4.8.3 Influence of SJL

The aim of our study was to determine if SJL can lead to more stress reactivity. Initially, we planned to assess 3 SJL groups but sample size did not allow for this. Instead, we split SJL into two groups, those with one hour or less SJL and those with greater than 1-hour SJL. We conducted three 2x2x3 mixed between within ANOVAs

to determine if SJL had any effect on changes in BP and BPM over the three time points. From the above analysis we know that there was a significant effect for time in the experimental group for all measures.

For systolic BP, there was no significant three-way interaction between group, time, and SJL, Wilks' Lambda = .967, $F(2,47) = .81$, $p = .452$. There was a significant interaction between time and SJL group, Wilks' Lambda = .834, $F(2,47) = 4.69$, $p = .014$, $\eta_p^2 = .166$. Post-hoc power analysis revealed that the power here was only .62. More participants are needed in future to investigate this interaction. Since there was no three-way interaction, we split the file by SJL group and performed two one-way ANOVAs. There was a significant effect of time in those with low SJL Wilks' Lambda = .207, $F(2,12) = 22.92$, $p < .001$, $\eta^2 = .79$ and those with high SJL, Wilks' Lambda = .431, $F(2,36) = 23.77$, $p < .001$, $\eta^2 = .57$ (see Figure 4.9).

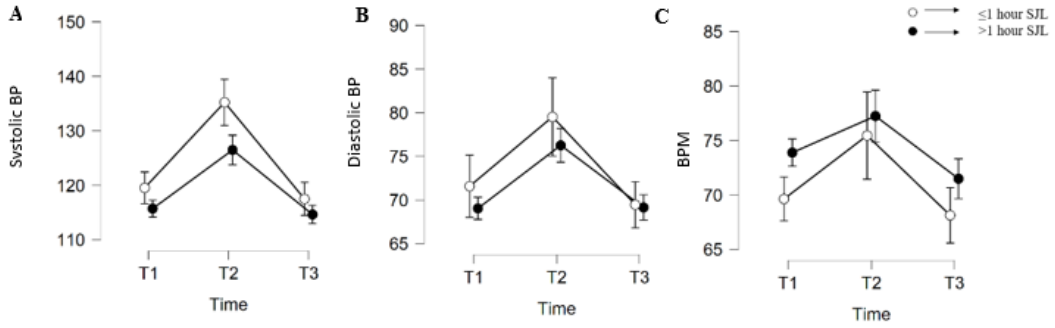
For diastolic BP, the interaction effect between group, time and SJL was significant, Wilks' Lambda = .874, $F(2,47) = 3.38$, $p = .042$, $\eta_p^2 = .126$. This finding was also underpowered (.62). Using G-power, in order to have a sufficiently powered study using this expected effect size a total sample size of 74 is required in future. This interaction was investigated in further detail to guide future research, but results need to be understood in the context of this power. As the previous analysis revealed a significant main effect of time in the experimental group but not controls, we again split the file, and conducted two two-way ANOVAs, one in controls and the other in the experimental group. In the experimental group there was no significant interaction between SJL group and time, Wilks' Lambda = .944, $F(2,25) = .74$, $p = .487$, $\eta_p^2 = .056$. The main effect of time was significant, Wilks' Lambda = .442, $F(2.25) = 17.16$, $p < .001$, $\eta_p^2 = .578$. In the controls there was no significant interaction between SJL group and time, Wilks' Lambda =.796, $F(2,21) = 2.69$, $p = .091$, $\eta_p^2 = .204$ or main effect of time, Wilks' Lambda = .945, $F(2,21) = .61$, $p = .554$, $\eta_p^2 = .055$). This suggests that the significant interaction may have been simply due to chance or that the subsamples were underpowered to probe the interaction.

For BPM, no significant three-way interaction was found between experimental group, time, and SJL, Wilks' Lambda = .965, $F(2,47) = .841$, $p = .438$. There was no interaction effect between time and SJL group, Wilks' Lambda = .959, $F(2,47) = 1.01$, $p = .371$. The association between SJL and the change in BP and BPM

between baseline and submersion and resting and submersion were assessed using Spearman's rho. No significant associations were identified in either controls of those in the experimental group.

Figure 4.9

Systolic BP, diastolic BP, and BPM during the task in those with low and high SJL.

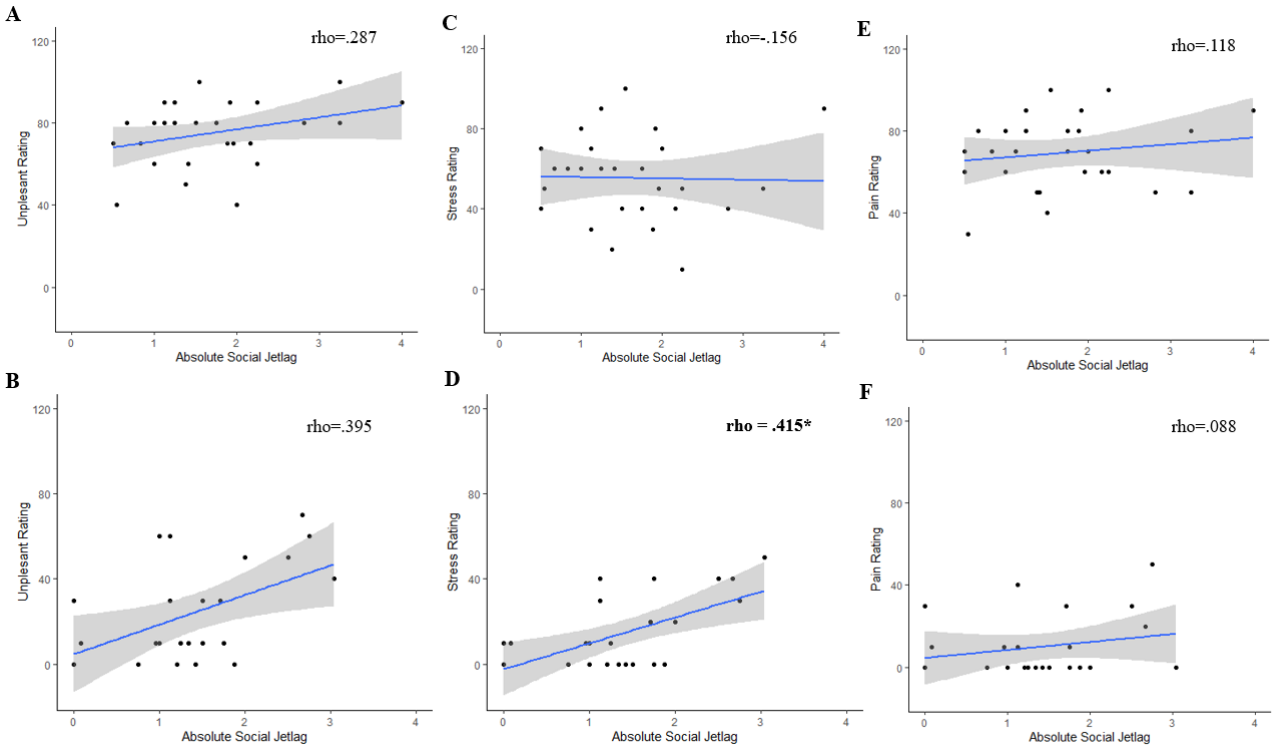


Note. T1 refers to baseline, T2 is during submersion (average of upon submersion and one minute following submersion) and T3 is after resting. Less than one-hour SJL is indicated by the open circles and greater than one-hour SJL are indicated by the closed circles on the figure as indicated by the figure legend. Figure A shows change in systolic BP for SJL groups over the three time points. For systolic BP a significant interaction between SJL group and time was observed and when investigated individually there was a larger effect in those with less than or equal one hour as observed in the diagram. Figure B shows the same but for diastolic BP and figure C shows this for BPM. No significant interaction between SJL and time were observed for diastolic BP or BPM. All figures include 95% error bars.

Further investigation of both groups identified that greater absolute SJL was not associated with any of the self-report variables in the experimental group. Greater absolute SJL was not associated with unpleasant or painful rating in controls. However, in the control group greater absolute SJL was associated with higher stress ratings (*rho* = .415, *p* = .044) and this was not significant in the experimental condition (*rho* = -.156, *p* = .428; see Figure 4.10). Interestingly SJL also showed no association with BMI. Notably, absolute SJL showed no relationship with the KSS the measure of sleepiness in the experimental (*rho* = .098, *p* = .618) or control group (*rho* = .035, *p* = .872).

Figure 4.10

Association between absolute SJL and unpleasantness rating in the experimental group (A) and the control group (B), stress rating in the experimental group (C), and the control group (D) and pain rating in the experimental group (E) and the control group (F). The only significant association was between greater SJL and stress in controls.



Note. SJL is reported here in hours.

In sum, SJL was not associated heart rate or the self-reported unpleasantness or pain. Those with less SJL showed larger changes in systolic BP and this was not contingent on experimental group. There was a three-way interaction between SJL group, experimental group, and time for diastolic BP. However, when investigated no significant interaction was found in either group, and the only significant main effect was as expected in the experimental condition. Those with more SJL did seem to find the SECPT more stressful in the control group, not the experimental one.

4.9 Discussion

Study 2 involved recruiting participants to take part in a stress-reactivity test and the objective was to assess if SJL was associated with greater reactivity to stress. There was two different conditions, both of which involved the socially evaluative component, and one with ice-cold water (experimental group) and the other with room temperature water (control group). For diastolic BP and heart rate there was an increase from baseline to during the task and a decrease then between the task and resting for the experimental group only. However, surprisingly for systolic BP there was an increase for both controls and the experimental group from baseline to the task and then a decrease to resting. Notably, the increase was much larger in the experimental group, but it's possible that the socially evaluative (psychological) component alone had an influence on systolic BP in our group of controls. Our participants did not know this was a control manipulation and it may have caused some uncertainty. Previous research by Schwabe et al. (2008) noted an increase in systolic BP in their socially evaluative warm water test, but to a lesser degree than their socially evaluative cold-water test. However, previous research by Minkely et al. (2014) has suggested that the cold water is necessary to elicit this response. Future studies with additional conditions could be carried out, for example the CPT and control CPT without the socially evaluative component could be added, but this would require more participants.

SJL among our undergraduate students who completed the SECPT was higher than the study 1 with the sample displaying 94 minutes of absolute SJL on average. This group was made up of predominantly young adults (average age was 23) with a few mature students. This is in line with previous research in young adults which has found that this group do experience a considerable amount of SJL (90 minutes average; Lanoye & LaRosa, 2020). Some previous research has suggested that eveningness may be associated with increased blood pressure measurements before and during a mental stress test, however this study did not assess SJL (Roeser et al., 2012).

SJL had no impact on two physiological measures of stress reactivity; diastolic BP and BPM. Interestingly, an interaction between high and low SJL with time was observed for systolic BP where both groups were significant but there was a stronger effect in the low SJL group. SJL, chronotype and the other sleep and circadian rhythm

measures were not associated with any of the baseline physiological measures of stress. This suggests that SJL does not have a big impact how an individual responds to a stressful situation. Notably, controls with higher SJL did self-report finding the experience more stressful while those in the experimental group did not. The reason for this is not immediately clear, especially considering that those with low SJL showed a larger physiological response. It is possible that the physiological stressor was more potent in the experimental group, and this distracted from any subjective stress they may have experienced. Interestingly, SJL also showed no association with BMI despite previous research suggesting that greater SJL and BMI are associated (Roenneberg et al., 2012). The majority of people in this study had a normal BMI and this small range may be why no association was observed.

4.9.1 Strengths and Limitations

In study 2 the use of SECPT is a strength as it is a well validated task for eliciting HPA axis activity as well as SNS reactions. Rich information was obtained from over 50 participants. While the SECPT enabled us to get rich data from 52 participants a larger sample size would have allowed the analysis of three rather than two SJL groups. This would have been optimal in order to confirm no significant interaction with group on outcome measures. Post-hoc power analysis suggested that these associations were underpowered (~.62) and that a larger sample was needed to achieve the desired level of power (.80).

4.10 General Conclusion

This chapter involved two studies and investigated the association between SJL, a measure of circadian misalignment, and perceived stress, work-related stress, and stress reactivity. Study 1 focused on the cross-sectional association between SJL and both perceived and work-related stress. Study 2 involved recruiting participants to take part in a stress-reactivity test and the objective was to assess if SJL was associated with greater reactivity to stress. This research has several strengths. It is one of a few studies that sets out to determine the relationship between SJL and general psychological stress, work-specific stress, and stress reactivity.

SJL does not significantly explain any variance in general psychological stress or components of the job demand-control-support model of work-related stress. Younger age, being female and having poorer sleep quality were significantly associated with displaying higher psychological stress. On the other hand, earlier chronotype and shorter average sleep duration were associated with higher decision latitude, while only age was associated with psychological demands. Greater SJL also did not have any impact on the stress reactivity. All these findings combined makes it unlikely that SJL was associated with higher stress in chapter 2 or that this explained any of the variance in HbA1c levels observed. The next chapter investigates sleep timing differences across the week and any associations with various sociodemographic variables in a large cohort of UK adults.

Chapter 5:

Exploring Week to Weekend Day Sleep Offset Differences: A UK Biobank Study.

The author would like to thank Dr. Cathy Wyse for processing the accelerometer data for this study.

Abstract

External social demands often force people to 'live against' their internal biological clock; this occurs severely with shift work or more mildly with social jetlag. This is extremely common in modern society and has been associated with a number of unhealthy lifestyle behaviours and health outcomes. The purpose of this research was to explore sleep offset advances or delays between week and weekend days a proxy measure of weekly circadian or sleep misalignment among this large cohort study (N = 79161, 57.3% female, mean age = 56.55). Participants displayed just over an hour of absolute weekday-weekend day sleep offset difference and over 30 minutes of actual weekday-weekend day sleep offset difference. Workers displayed greater absolute ($p < .001$, Cohens $d = .31$) and actual ($p < .001$, Cohens $d = .39$) weekday-weekend day sleep offset difference than those not working; those not working did however display a large range of weekday-weekend day sleep offset difference. When stratified by age (39-49; 50-59; 60-70) younger participants had greater weekday-weekend day sleep offset difference. Interestingly, those with the greatest weekday-weekend delay had the shortest self-reported sleep duration in all three age categories while longer sleep duration was reported in those with the greatest weekday-weekend day sleep offset advance. Physical activity also did not differ between groups in those aged between 39 and 49 or 50 and 59 but among the oldest participants those with low weekday-weekend day sleep offset difference (0-1 hour) had the highest physical activity in comparison to all other groups. This research demonstrated how social factors are influencing peoples sleep timing either on weekdays or weekend days resulting in delayed or advanced sleep timing across the week.

Keywords: Sleep offset differences, social jetlag, work status, age, physical activity, chronotype.

5.1 Introduction

SJL is a growing aspect of sleep research and has a global prevalence, however, SJL is sometimes considered a secondary outcome measure rather than the primary one (Henderson et al., 2019). Research has identified that around 80% of people use alarm clocks on workdays meaning they do not wake naturally and are arising during their biological night (Roenneberg et al., 2015). Notably, at least one hour of SJL is reported in 69% of individuals while over 2 hours is reported in 33% of individuals (Roenneberg et al., 2015). Hashizaki et al. (2015) noted a 40-minute delay in midsleep time, a 26-minute delay in bedtime and a 53-minute delay in wake time between weekdays and weekend days, concluding that social obligations and work often restrict or disturb peoples sleep patterns. Jonasdottir et al. (2021) carried out some interesting research and identified that sleep onset and offset advance with age with people sleeping and waking earlier as they get older. The difference between weekday and weekend day onset and offset also decreased steadily with age, but slightly more rapidly from 55-59 years and 60-67 years which overlaps with typical retirement age. This added some valuable findings despite having no information on work schedules. It also pointed toward the fact that we cannot assume that older adults will have standard week/weekend day schedules as some variations in sleep timing persist into retirement.

When evaluating the consequences of SJL, the absolute value is mainly utilised (Roenneberg et al., 2012). However, the actual difference, which includes negative values, may also be important (Roenneberg et al., 2019). The distribution of the actual difference is also less skewed than the distribution of the absolute difference (Roenneberg et al., 2019). Negative SJL reflects an earlier midsleep timing on free days than workdays, suggesting that social obligations might be keeping this group up later than their internal biological clock during the week. There are currently few descriptions of negative SJL (Kohyama, 2017) and it is unknown if positive and negative SJL have a similar effect on health. A recent cross-sectional Japanese study of SJL identified that only 6% of the overall population displayed negative SJL, this was reflective of only 3% of people in their 20's and 8.6% of people in their 60's (Komada et al., 2019). McMahon et al. (2018) carried out a study on sleep disruption and SJL, calculating both the absolute and relative value. 14.3 % of this sample of 21–35-year-olds had negative SJL. Both of these studies suggest that negative SJL is less

common than positive SJL and that younger participants are less likely to experience negative SJL, potentially due to the fact that they are more likely to display a later chronotype. It is important to determine if the effect of SJL on health is linear or if negative and positive SJL have a similar impact (Henderson et al., 2019). This is something that has not been clearly done in the past, partly due to ambiguity surrounding the calculation of SJL and the majority of studies reporting absolute SJL only.

The current study calculated weekday/weekend day sleep offset differences, as information on workdays and work free days was not available. Previous research has also used weekdays to signify workdays and weekend days to signify work free days when that data was not available (Jonasdottier et al., 2021; Kuula et al., 2019). Furthermore, research has suggested that around 75% of the US and European population work Monday through Friday (Bureau of labor statistics, 2019; Eurofound, 2012). Weekday-weekend day sleep offset differences were examined as both its actual and absolute form. There is value in focusing on sleep offset differences because individuals have practical control over the time they wake up at and it may be easier to change than midsleep timing (Jonasdottir et al., 2021). Actual weekday-weekend day differences described whether people displayed an advance or delay in sleep timing from weekdays to weekend days, with positive values indicating a delay and negative values indicating an advance. Absolute weekday-weekend day differences on the other hand just described the difference in terms of distance from zero so no negative values were included.

The aim of the current study was to analyse the distribution of both actual and absolute weekday-weekend day sleep offset differences in this large sample provided by the UK Biobank, in order to get a clear overview of sleep offset advances and delays. The second aim was to explore any differences between demographic, behavioural and metabolic health-related outcomes among participants with positive and negative weekly sleep offset differences. Based on previous research it was hypothesised that actual weekday-weekend day sleep offset differences would be less skewed than the absolute value. It was also hypothesised that workers, people with a later chronotype and those with higher levels of deprivation would display higher levels of both actual and absolute sleep offset differences. Differences in metabolic variables between the levels of sleep offset differences were assessed in order to

determine if positive and negative weekday-weekend day sleep offset differences were having differing effects. No hypothesis was developed here due to the exploratory nature of the study and the limited previous research.

5.2 Methods

5.2.1 Sample

The study sample were participants who took part in the UK Biobank study. Over 500,000 participants in the National Health Service registry in the UK were recruited as part of this study between 2006 and 2010 (UKB handbook). A subset of these participants wore wrist activity monitors for 7 days and inclusion in this current study was restricted its analysis to those who had good actigrams (i.e.) sufficient weekend day and weekday data so that sleep offset differences could be analysed. This study was covered by the generic ethical approval for UK Biobank studies from the NHS National Research Ethics Service (approval letter dated 17th June 2011, Ref 11/NW/0382) for project #26209 (PI Wyse). All participants provided their full informed consent to participate in the UK biobank research and to have their data analysed for all extending research. This research was also approved by the Maynooth University Social Research Ethics Sub-Committee.

5.2.2 Participant Measures

Participants attended one of the 22 assessment centres across the UK. At baseline, all participants completed numerous touchscreen questionnaires, interviews, and anthropometric assessments. Blood samples were also provided at baseline. Demographics included are age, sex (male/female) and ethnicity (White, Black, Mixed, Chinese, Asian, Other), which were self-reported by a touch-screen questionnaire. Townsend deprivation index based on postcode of residence was calculated for each participant as a measure of socioeconomic status, this was split into quintiles to aid analysis. Chronotype was self-reported, and individuals answered the question “Do you consider yourself to be …" with one of the following responses: definitely a morning person, more of a morning person than an evening person, more of an evening person than a morning person or definitely an evening person. Some individuals also reported ‘do not know’ or ‘prefer not to answer’ and for the purpose of this analysis these were coded as missing responses. Sleep duration was also self-reported in hours per 24 hours. Total physical activity measured as metabolic equivalents (MET. hours/week) was calculated from self-reported duration and intensity of usual physical activity. Average alcohol intake was reported as never, special occasions only, 1-3 times per month, 1-2 times per week, 3-4 times per week

and daily/almost daily. Smoking status was categorised as current smoker or non-smoker. Light at night (LAN) at home was measured as intervals of the greyscale of tiff files. This was put into four categories with 1 referring to low light, 2 referring to medium light, 3 referring to high light and 4 referring to max light. Information on work status was also collected with individuals either being classed as currently working or not working. Currently working encompasses those in full and part time employment. Anthropometric measures including BMI (kg/m^2), and systolic and diastolic blood pressure were assessed at baseline by trained UK Biobank staff using standardised instruments and measurements. HbA1c was measured by HPLC analysis on a Bio-Rad VARIANT II Turbo from biological samples obtained.

5.2.3 Sleep Offset Differences between Week and Weekend Days

Sleep offset times on weekdays (Tuesday – Thursday) were subtracted from sleep offset times on weekend days (Saturday and Sunday). Sleep offset values were obtained from participants activity monitors. Participants wore an axivity AX3 wrist-worn triaxial accelerometer on their dominant hand for 7 days. These physical activity monitors were worn by a subset of participants between June 2013 and January 2016. The data this collected was analysed using the ClockLab software to assess sleep offset times. Our measure of weekday-weekend day sleep offset differences was assessed in both actual and absolute terms. The raw difference including negative values is known as actual weekday-weekend day sleep offset differences, while the absolute difference simply describes its distance from zero, so there are no negative values. Both of these measures capture sleep offset differences in the sample.

5.2.4 Statistical Analysis

This exploratory analysis was conducted using IBM SPSS version 25 and RStudio. The main variables of interest were absolute and actual weekday-weekend day sleep offset differences. The distribution of each were examined to determine if this was in line with previous research. Absolute and actual weekday-weekend day sleep offset differences were firstly examined as continuous variables and groupwise analysis was conducted with work status, chronotype, and deprivation quintiles. Actual weekday-weekend day sleep offset difference was then grouped into five categories to examine any differences in the demographic, lifestyle, sleep, or health measures between the groups. This allowed for the evaluation of the influence of

positive and negative sleep offset differences. However, many health variables of interest in this sample are known to be age dependent. For ths reason, we stratified the sample by age and the differences in health, and sleep variables were assessed in people in their 40's, 50's, and 60's separately.

Parametric statistics were utilised throughout due to the large sample size which accounts for slight deviations from normality. Research has suggested that t-tests and F-tests are both robust tests and can be used when the data deviates from normality if there is a large sample size (Blanca Mena et al., 2017; Fagerland, 2012). The large sample and number of participants in groups should limit any effect this deviation from normality has. Independent samples t-tests with Cohens *d* effect estimates were used when comparing two groups and one-way ANOVA's and η^2 estimates of effect size were used to compare variables with more than two levels. Chi square test of independence was used to examine the relationship between categorical variables (i.e.) the grouped weekday-weekend day sleep offset differences and chronotype / work status. Hierarchal regression analysis was used to examine the relative associations of demographic, sleep and cardiometabolic factors with absolute weekday-weekend day sleep offset differences. Graphs were created on r studio, and raincloud plots were created by adapting code from Allen et al. (2019).

5.2.5 Data Screening

The full sample available with a measure of weekday-weekend day sleep offset differences was 87,590. Information on shift work was only available for 61.5% of the sample (*N* = 53,878 with 33,712 missing). Of these only 6820 (7.8%) engaged in shift work. All the individuals who said they engaged in shift work were excluded from the sample leaving the new sample size at 80,770. The data was further cleaned for outliers in some of our key variables. Those with less than 3 and more than 13 hours self-reported sleep duration per night were excluded (*N* = 26). BMI < 12, > 60 or not reported were also excluded from our analysis (*N* = 206), this is in line with Roenneberg et al., (2012) exclusion criteria. In terms of the measure of actual week to weekend day sleep offset differences those outside of three standard deviations of the mean were also excluded (*N* = 744), as we did not have information on work schedule, and it is likely that these outliers were working weekends. Of the remaining 79,793 we removed a further 557 with no information on work status. Following on from this

there were only 75 participants who identified as working with no information of shift working status, these 75 were removed which allowed us to proceed with a final sample of N = 79,161, cleaned for shift workers, and other extreme variables. Those with physical activity measures more than three standard deviations away from the mean were also coded as missing as they were unrealistic. There were complete observations for actual and absolute weekday-weekend day sleep offset differences, age, sex, work status and BMI in this sample. Sample size does vary for some variables, but this is noted throughout.

5.3 Results

5.3.1 Descriptives

Demographics and descriptive statistics of the 79,161 participants included in the analysis are detailed in Table 5.1. 57.3% were female, 97.3% were white, and the average age was 56.55 years (*SD* = 7.79). The average BMI was 26.61 (*SD* = 4.46), 3.4% of participants had a diagnosis of diabetes, and 93.6% identified as non-smokers. 41.3% were not currently working, and those currently working were significantly younger (*M* = 53.01 yrs, *SE* = 0.032) than those who were not working (*M* = 61.58 yrs, *SE* = 0.033, $p < .001$). The average self-reported sleep duration was 7:11h (*SD* = 0:58), and 25.5% were identified as morning types, 38.2% more morning than evening, 27.4% more evening than morning and 8.8% evening types.

Table 5.1

Demographics, health, and sleep characteristics of the study sample.

	Sample Size	% or mean (SD)
Sociodemographic variables		
Age	79,161	56.55 (7.79)
Sex	79,161	
Female	45,353	57.3%
Male	33,808	42.7%
Deprivation Index	79,072	-1.82 (2.77)
Quintile 1	15,859	-4.83 (.55)
Quintile 2	15,767	-3.59 (.30)
Quintile 3	15,813	-2.50 (.34)
Quintile 4	15,819	-0.87 (.64)
Quintile 5	15,814	2.71 (1.82)
Ethnicity	78,944	
White	76,840	97.3%
Mixed	391	0.5%
Asian	657	0.8%
Black	507	0.6%
Chinese	174	0.2%
Other	375	0.5%
Work Status	79,161	
Working	46,438	58.7%
Not working	32,723	41.3%
Health-related Variables		
BMI (kg/m^2)	79,161	26.61 (4.46)
Smoker:	78,991	
Yes	5037	6.4%
No	73,954	93.6%
Alcohol:	79,128	
Never	4304	5.4
Special occasions only	7297	9.2
1-3 times pm	8377	10.6
1-2 times pw	19,669	24.9
3-4 times pw	20,936	26.5
Daily/Almost daily	18,545	23.4
Physical Activity	77,576	35.91 (35.66)
Sedentary time	79,105	4.89 (2.13)
DM	2697	3.4%
HbA1c (mmol/mol)	74,106	35.39 (5.50)
SBP (mm hg)	75,537	138.76 (19.34)
DBP (mm hg)	75,538	81.58 (10.56)
Sleep-related variables		
Actual Weekday-Weekend Difference (h:mm)	79,161	00:34 (01:13)
Absolute Weekday-Weekend Difference (h:mm)	79,161	1:03 (00:50)
Sleep Duration (h:mm)	78,992	7:11 (00:58)

5.3.2 Weekday and Weekend Sleep Offset Differential

The mean absolute and actual differences between sleep offset (wake time) on weekdays (WD; Tuesday, Wednesday, and Thursday) versus weekend days (WE; Saturday and Sunday) were 1:03h (range 0 to 4:26h, *SD* = 0:50h) and 0:34h (range -3:18h to 4:26h, *SD* = 1:13h; Figure 5.1). Males had greater absolute and actual WD/WE sleep offset differences than females (*M* = 1:04h, *SE* = 0:17m vs *M* = 1:02h, *SE* = 0:14m, $p < .001$, Cohen's *d* = .04 for absolute and *M* = 0:35h, *SE* = 0:24m vs *M* = 0:33h, *SE* = 0:20m, $p = .002$, Cohen's *d* = .02 for actual; Figure 5.2). Participants not in work had significantly lower absolute and actual WD/WE differences compared to those working (*M* = 0:54h, *SE* = 0:15m vs *M* = 1:09h, *SE* = 00:15 m, $p < .001$, Cohen's *d* = .31 for absolute and *M* = 0:18h, *SE* = 0:22m vs *M* = 0:45h, *SE* = 0:21m, $p < .001$, Cohen's *d* = .38 for actual WD/WE differences; Figure 5.3). Age also was associated with WD/WE sleep offset differential, with younger participants (39-49 years) showing greater absolute differences than older groups (50-59 years and 60-70 years; *M* = 1:19h, *SE* = 0:26m vs *M* = 1:04h, *SE* = 0:18m and *M* = 0:53h, *SE* = 0:14m, $p < .001$, $\eta^2 = .04$; Figure 5.2). Those aged 50-59 also displayed greater absolute WD/WE sleep offset differential than those aged 60-70. Younger participants (39-49 years) also showed greater actual differences than older groups (50-59 years and 60-70 years; *M* = 1:00h, *SE* = 0:35m vs *M* = 0:37h, *SE* = 0:26m and *M* = 0:17h, *SE* = 0:22m, $p < .001$, $\eta^2 = .05$; Figure 5.2). Similar to the absolute differences those aged 50-59 also displayed greater actual WD/WE sleep offset differential than those aged 60-69.

Figure 5.1

(A) Distribution of absolute and (B) actual WD/WE sleep offset differences in the study sample.

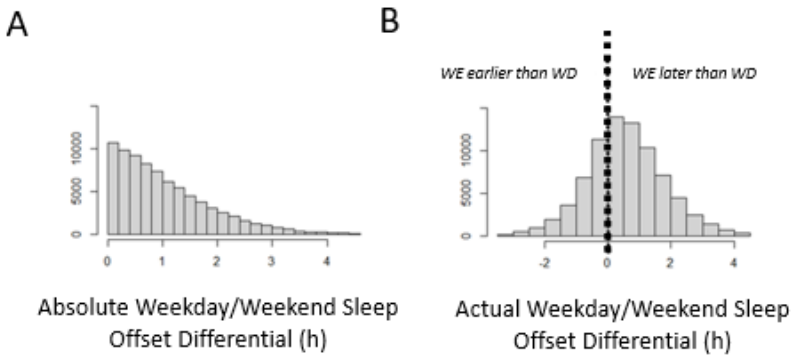


Figure 5.2

Raincloud plots of the distribution of absolute and actual WD/WE sleep offset differences by sex (A) and age group (B).

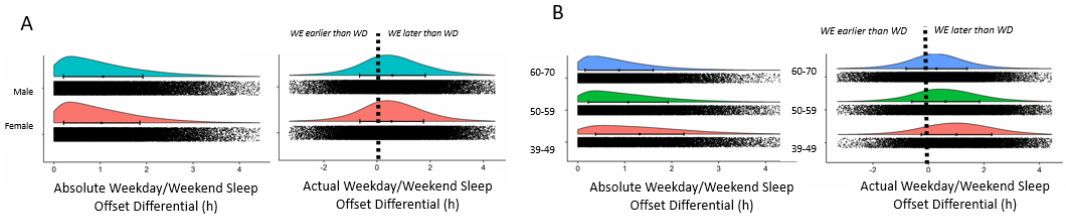
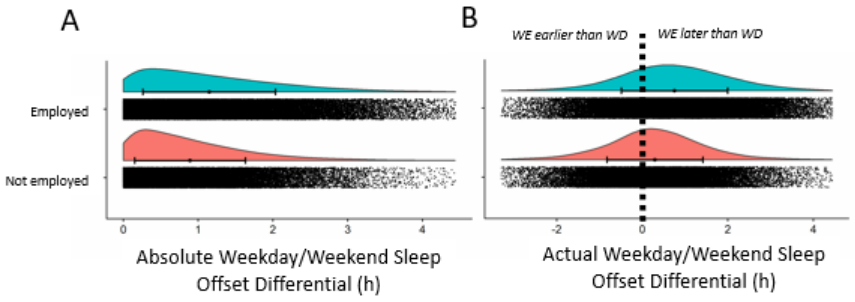


Figure 5.3

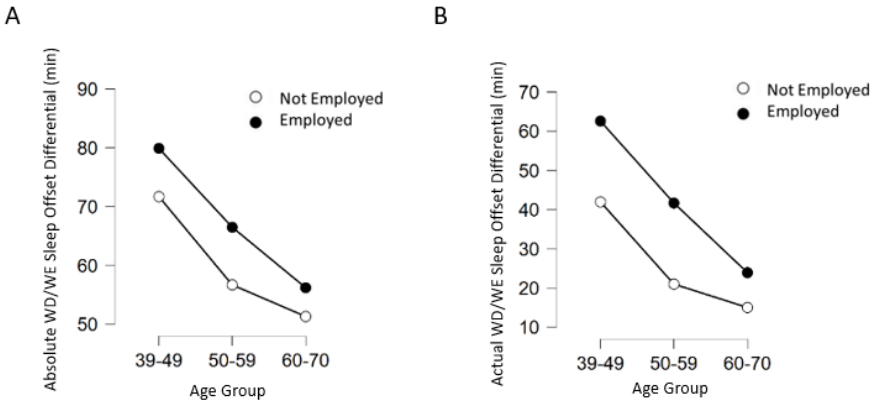
Raincloud plots of the distribution of absolute (A) and actual (B) WD/WE sleep offset differences by employment status.



Since employment plays a role in misalignment a 2x3 between groups ANOVA was conducted for actual WD/WE sleep offset differences. A significant interaction was observed between age group and work status, $F(_{2, 79,155}) = 46.28$, $p < .001$, $\eta_p^2 = .001$. Due to this interaction, we split the file by our variable with the least levels (work-status) and conducted two separate one-way ANOVAs. A significant main effect of age was found in those not working $F(_{2, 32,720}) = 150.89$, $p < .001$, $\eta^2 = .009$, and those working $F(_{2, 46,435}) = 858.29$, $p < .001$, $\eta^2 = .036$. The same analysis was conducted for absolute WD/WE sleep offset differences. A significant interaction was observed, $F(_{2, 79,155}) = 14.66$, $p < .001$, $\eta_p^2 < .001$. Due to this interaction, we again split the file by work-status and conducted two separate one-way ANOVAs. A significant main effect of age was found in those not working $F(_{2, 32,720}) = 206.70$, $p < .001$, $\eta^2 = .012$, and those working $F(_{2, 46,435}) = 636.80$, $p < .001$, $\eta^2 = .027$. There was a larger effect size in those working, however, the age-related decrease in WD/WE sleep offset differences was present in both participants who were employed and also in those not working, indicating that the age-related decrease was not purely ascribable to greater proportions of older participants not being in work (Figure 5.4).

Figure 5.4

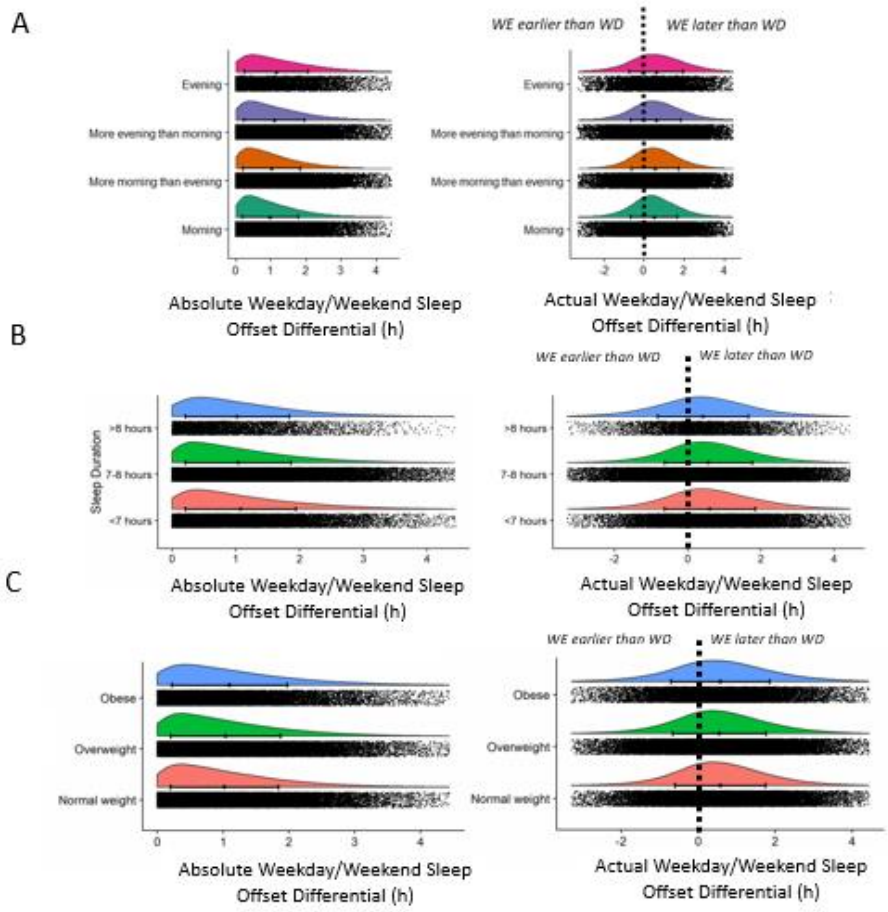
(A) Absolute WD/WE sleep offset difference for age group and employment status (B) Actual WD/WE sleep offset difference for age group and employment status.



Evening chronotypes had the greatest absolute and actual WD/WE difference in sleep offsets ($F_{(3, 70,666)} = 104.79$, $p < .001$, $\eta^2 = .004$ for absolute values and $F_{(3, 70,666)} = 29.68$, $p < .001$, $\eta^2 = 001$ for actual values; Figure 5.5A). When examined in three age groups (as chronotype is strongly affected by age), participants actual WD/WE sleep offset difference had the least representation of morning types in 39- to 49-year-olds, 50- to 59-year-olds and 60- to 70-year-olds (Table 5.2). When examined by sleep duration, participants who slept less than 7 hours a night had the greatest absolute WD/WE sleep offset difference (*M* = 1:05h, *SE* = 0:24m) in comparison to those who slept 7-8 hours (*M* = 1:02h, *SE* = 0:12m) and more than 8 hours (*M* = 1:01h, *SE* = 0:41m), $F_{(2, 78,989)} = 16.51$, $p < .001$, $\eta^2 < .001$; Figure 5.5B). The same was observed for actual WD/WE sleep offset difference whereby those who slept less than 7 hours had the greatest WD/WE sleep offset difference (*M* = 0:36h, *SE* = 0:35m), when compared to those with 7-8 hours (*M* = 0:34h, *SE* = 0:18m) and more than 8 hours (*M* = 0:25h, *SE* = 1:03m), $F_{(2, 78,989)} = 47.64$, $p < .001$, $\eta^2 = .001$; Figure 5.5B). Participants with > 2h WD/WE sleep offset difference had the shortest sleep duration in each of the three age groups examined (Table 5.2).

Figure 5.5

(A) Raincloud plots of the distribution of absolute and actual WD/WE sleep offset differences by chronotype; (B) Raincloud plots of the distribution of absolute and actual WD/WE sleep offset differences by sleep duration group; (C) Raincloud plots of the distribution of absolute and actual WD/WE sleep offset differences by BMI group.



Note. N = 440 underweight participants excluded from this graph.

Table 5.2

Sleep and chronotype as a function of age group and actual WD/WE sleep offset difference group.

WD/WE Group:	1 (>-1h)	2 (-1h; 0h)	3 (0h; 1h)	4 (1h; 2h)	5 (>2h)	P
Age: **<u>39-49yrs</u>**						
Sleep duration	7:17h (1:58m) **3,4,5*	7:14h (1:03m) **5*	7:10h (0:45m) **1,5*	7:10h (0:44m) **1,5*	7:07h (0:54m) **1,2,3,4*	<.001
Chronotype, % M	20.7	23.0	23.4	21.9	18.2	<.001
Chronotype, % E	15.0	11.4	9.6	10.7	12.9	<.001
Age: **<u>50-59yrs</u>**						
Sleep duration	7:10h (1:16m) **4,5*	7:09h (0:44m) **4,5*	7:07h (0:35m) **5*	7:05h (0:42m) **1,2,5*	7:01h (0:57m) **1,2,3,4*	<.001
Chronotype, % M	24.6	26.0	26.9	25.5	22.6	<.001
Chronotype, % E	10.6	8.6	7.9	8.7	11.2	<.001
Age: **<u>60-70yrs</u>**						
Sleep duration	7:19h (1:03m) **2,3,5*	7:15h (0:37m) **1*	7:15h (0:32m) **1*	7:16h (0:48m)	7:13h (1:24m) **1*	.001
Chronotype, % M	26.8	27.7	28.4	26.1	24.9	<.001
Chronotype, % E	8.4	7.5	6.8	8.0	9.4	<.001

Note. Data are M ± SE analysed via one-way ANOVA for sleep duration. Chi square analysis conducted for chronotype, and data are percentage per group.

Obese participants had greater WD/WE sleep offset differences than overweight and normal weight participants only when it was expressed in absolute, and not actual, terms (M = 1:06h, SE = 0:26m vs M = 1:02h, SE = 0:17m and M = 1:01h, SE = 0:17m, $F(_{2,\ 78,718}) = 43.81$, $p < .001$, η^2=.001. No significant difference was observed for actual WD/WE sleep offset differences, $F(_{2,\ 78,718}) = 3.10$, $p = .05$, η^2<.001; Figure 5.5C). When examined according to the Townsend Deprivation Index, participants in the most deprived quintile experienced greater absolute WD/WE sleep offset difference (M = 1:07h, SE = 0:25m, $F(_{4,\ 79,067}) = 43.91$, $p < .001$, η^2=.002) and

greater actual WD/WE sleep offset difference (*M* = 0:38h, *SE* = 0:36m), $F(_{4,\ 79,067}) =$ 19.19, $p < .001$, $\eta^2 = .001$), in comparison to the four other quintiles. The fourth quintile also had greater absolute (*M* = 1:03h, *SE* = 0:24m) and actual (*M* = 0:35h, *SE* = 0:35m) WD/WE differences than quintile 1-3 but less than quintile 5; Figure 5.6A, Table 5.3). Participants whose residence were in areas of high light-at-night (LAN) also experienced greater absolute WD/WE difference than those with lower LAN (*M* = 1:05h, *SE* = 0:18m vs *M* = 1:01h, *SE* = 0:13m; $p < .001$, Cohen's $d = .08$) and actual WD/WE difference (*M* = 0:37h, *SE* = 0:26m vs *M* = 0:32h, *SE* = 0:20m), $p < .001$, Cohen's $d = .06$; Figure 5.6B, Table 5.3). Participants who were smokers displayed greater absolute WD/WE sleep offset differences than non-smokers (*M* = 1:09h, *SE* = 0:46m vs *M* = 1:02h, *SE* = 0:11m, $p < .001$, Cohen's $d = .14$) and greater actual WD/WE sleep offset differences (*M* = 0:38h, *SE* = 1:07m vs *M* = 0:33h, *SE* = 0:16m, $p < .001$, Cohen's $d = .06$). Those who were of non-white ethnicity also had greater levels of absolute and actual WD/WE sleep offset differences (*M* = 1:13h, *SE* = 1:13m vs *M* = 1:02h, *SE* = 0:11m, $p < .001$, Cohen's $d = .21$ for absolute; *M* = 0:45h, *SE* = 1:45m vs *M* = 0:33h, *SE* = 0:16m, $p < .001$, Cohen's $d = .16$ for actual; Table 5.3; Figure 5.7).

Figure 5.6

(A) Raincloud plots of the distribution of absolute and actual WD/WE sleep offset differences by deprivation index quintiles; (B) Raincloud plots of the distribution of absolute and actual WD/WE sleep offset differences by light-at-night (LAN) categories.

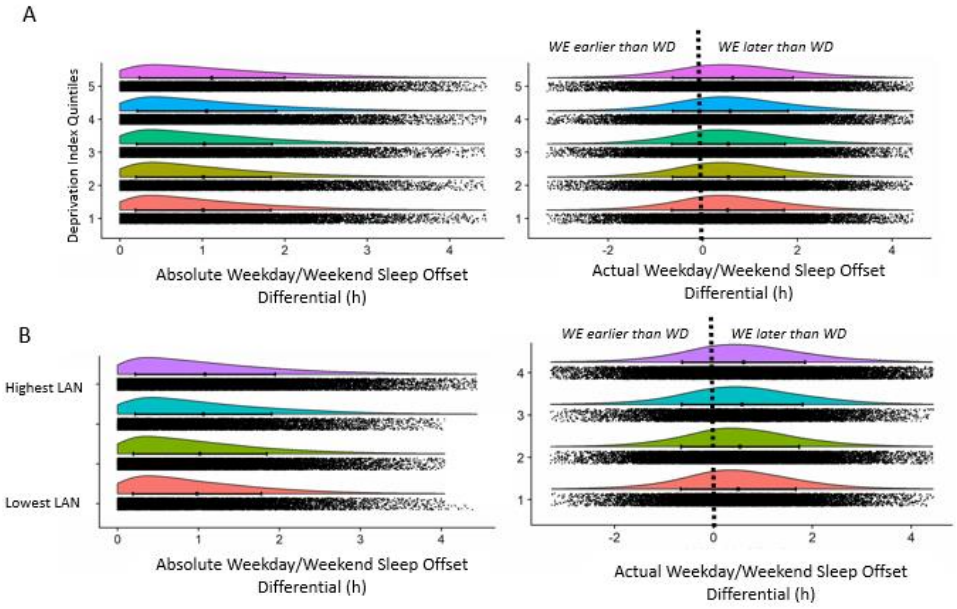


Table 5.3

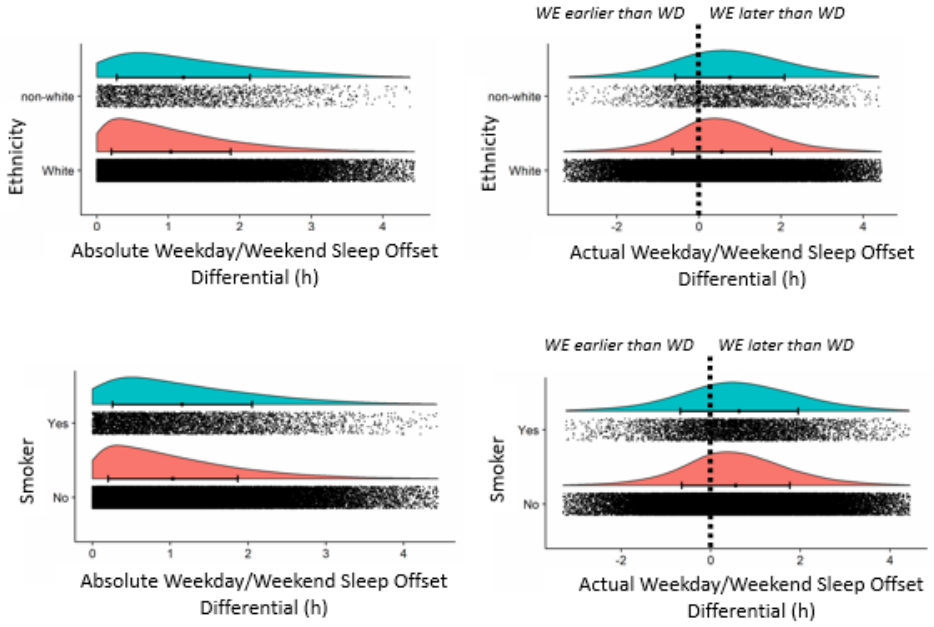
Demographics of the participants as categorised into five groups according to their actual WD/WE sleep offset differences.

WD/WE Group	1(≥ 1 h)	2(-1h; 0h)	3(0h; 1h)	4(1h; 2h)	5(>2h)	p
N, (%)	**7026, (8.9)**	**18013, (22.8)**	**27323, (34.5)**	**17505, (22.1)**	**9294 (11.7)**	
Sex (% female)	57.2	57.6	57.6	58.0	54.5	<.001
Age (years)	58.38 (0.086) *3,4,5	58.29 (0.054) *3,4,5	57.37 (0.046) *1,2,4,5	54.94 (0.060) *1,2,3,5	52.45 (0.079) *1,2,3,4	<.001
% Employed	47.2	50.4	55.3	66.8	77.7	<.001
Ethnicity (% white)	97.4	97.6	97.7	97.2	95.9	<.001
Deprivation Index	-1.77 (0.033) *2,3,5	-1.89 (0.020) *1,4,5	-1.92 (0.016) *1,4,5	-1.76 (0.021) *2,3,5	-1.52 (0.030) *1,2,3,4	<.001
Most deprived	20.7	19.0	18.7	20.7	23.9	<.001
Least deprived	19.9	20.6	20.7	19.3	18.5	<.001
Diabetes (% yes)	4.5	3.4	3.1	3.3	3.5	<.001
Smoker (% yes)	7.1	5.8	5.8	6.6	8.2	<.001
LAN (% Highest Category)	37.9	37.2	37.2	39.6	42.4	<.001

Note. Data are M ± SE or percentage. Statistical significance is indicated according to ANOVAs for continuous variables or chi-square tests for independence for categorical variables.

Figure 5.7

(A) Raincloud plots of the distribution of absolute and actual WD/WE sleep offset differences by ethnicity (white or non-white); (B) Raincloud plots of the distribution of absolute and actual WD/WE sleep offset differences by smoking status.



5.3.3 Association of WD/WE Sleep Offset Difference with Cardiometabolic Health

For the analysis of the associations between WD/WE sleep offset differences and cardiometabolic outcomes, we stratified participants by age (39-49 years, 50-59 years, and 60-70 years) as the cardiometabolic outcomes were affected by age. In order to account for violations to the assumption of homogeneity a p value of $p < .01$ was adopted for all two-way ANOVA analysis presented here. A two-way between groups ANOVA revealed no significant interaction between age groups and actual WD/WE sleep offset difference categorised into five levels (>-1h, -1h to 0h, 0h to1h, 1h to 2h and >2h) on BMI, $F(8, 79{,}146) = 2.36$, $p = .016$, $\eta_p^2 < .001$. There was a main effect of age group, $F(2, 79{,}146) = 123.27$, $p < .001$, $\eta_p^2 = .003$ and WD/WE differentials $F(4, 79{,}146) = 41.22$, $p < .001$, $\eta_p^2 = .002$. BMI varied according to the actual misalignment levels in each of the age groups (Table 5.4, Figure 5.8). A two-way ANOVA revealed no significant interaction between age group and actual WD/WE sleep offset differential

for HbA1c, $F(_{8, 74,091}) = .67$, $p = .715$, $\eta_p^2 < .001$. There was, however, a main effect of age, $F(_{2, 74,091}) = 1220.49$, $p < .001$, $\eta_p^2 = .032$, and of the actual WD/WE sleep offset differential, $F(_{4, 74,091}) = 4.18$, $p = .002$, $\eta_p^2 < .001$. A two-way ANOVA revealed no significant interaction between age group and actual WD/WE sleep offset differential grouped for systolic blood pressure, $F(_{8, 74,522}) = 1.23$, $p = .274$, $\eta_p^2 < .001$ meaning that systolic blood pressure did not vary across WD/WE sleep offset difference groups in any of the age groups. There was a main effect of age $F(_{2, 74,522}) = 2668.71$, $p < .001$, $\eta_p^2 = .067$. The main effect of WD/WE differentials was not significant. A two-way ANOVA also revealed no significant interaction between age group and actual WD/WE sleep offset differential grouped for diastolic blood pressure $F(_{8, 74,523}) = .919$, $p = .499$, $\eta_p^2 < .001$. There was a main effect of age group, $F(_{2, 74,523}) = 196.08$, $p < .001$, $\eta_p^2 = .005$ and WD/WE sleep offset differential grouped, $F(_{4, 74,523}) = 5.77$, $p < .001$, $\eta_p^2 < .001$ (Figure 5.8). No significant interaction between age group and WD/WE sleep offset differentials was observed for physical activity $F(_{8, 77,561}) = 1.75$, $p = .082$, $\eta_p^2 < .001$. There was a main effect of age group $F(_{2, 77,561}) = 98.11$, $p < .001$, $\eta_p^2 = .003$ and WD/WE sleep offset difference $F(_{4, 77,561}) = 4.41$, $p = .001$, $\eta_p^2 < .001$ (Table 5.4, Figure 5.8). Interactions between WD/WE sleep offset difference grouped and categorical variables can be observed in Figure 5.9.

Table 5.4

Cardiometabolic measures stratified by age and actual WD/WE sleep offset difference.

WD/WE Group:	**1 (>-1h)**	**2 (-1h; 0h)**	**3 (0h; 1h)**	**4 (1h; 2h)**	**5 (>2h)**	**P**
Age: 39-49yrs						
Sample size	1010	2752	5058	4998	3731	
BMI	**26.51 (0.15) *3,4**	**26.10 (0.09) *5**	**25.99 (0.06) *1,5**	**26.00 (0.06) *1,5**	**26.48 (0.08) *2,3,4**	**<.001**
HbA1c	33.59 (0.16)	33.36 (0.09)	33.48 (0.08)	33.44 (0.08)	33.53 (0.08)	.669
SBP	129.83 (0.56)	129.46 (0.34)	129.25 (0.24)	129.24 (0.24)	130.16 (0.27)	.079
DBP	**80.08 (0.37)**	**79.87 (0.22)**	**79.82 (0.15)**	**79.55 (0.15) *5**	**80.43 (0.18) *4**	**.006**
PA	34.66 (1.07)	36.11 (0.71)	35.13 (0.48)	35.31 (0.48)	33.69 (0.55)	.068
Age: 50-59yrs						
Sample size	2341	6115	9436	6543	3554	
BMI	**27.02 (0.10) *2,3,4**	**26.48 (0.06) *1,5**	**26.51 (0.05) *1,5**	**26.66 (0.06) *1,5**	**26.98 (0.08) *2,3,4**	**<.001**
HbA1c	**35.51 (0.12)**	**35.17 (0.07)**	**35.19 (0.05)**	**35.18 (0.07)**	**35.39 (0.10)**	**.030**
SBP	137.86 (0.39)	136.92 (0.24)	137.19 (0.20)	136.81 (0.23)	136.70 (0.31)	.113
DBP	82.33 (0.23)	81.85 (0.14)	82.02 (0.11)	82.15 (0.14)	82.33 (0.18)	.167
PA	33.09 (0.71)	33.41 (0.44)	33.53 (0.35)	33.68 (0.43)	32.48 (0.57)	.509
Age: 60-69						
Sample size	3675	9326	12829	5964	2009	
BMI	**27.16 (0.07) *2,3,5**	**26.73 (0.04) *1,5**	**26.64 (0.04) *1,4,5**	**26.92 (0.06) *3,5**	**27.55 (0.10) *1,2,3,4**	**<.001**
HbA1c	36.59 (0.10)	36.42 (0.06)	36.45 (0.05)	36.53 (0.08)	36.81 (0.15)	.053
SBP	145.16 (0.33)	144.71 (0.21)	145.18 (0.18)	144.43 (0.25)	144.91 (0.44)	.131
DBP	**82.24 (0.18)**	**81.95 (0.11) *5**	**81.91 (0.10) *5**	**82.03 (0.14)**	**82.68 (0.24) *2,3**	**.028**
PA	**37.68 (0.62) *3**	**38.12 (0.39) *3**	**39.70 (0.34) *1,2,4,5**	**37.67 (0.49) *3**	**36.75 (0.86) *3**	**<.001**

Note. Data are M ± SE. * Indicates post-hoc significant differences between the actual WD/WE sleep offset difference groups. BMI expressed in kg/m², HbA1c in mmol/mol, SBP and DBP in mmHg and physical activity (PA) in MET hrs/week.

Figure 5.8

Age group x actual WD/WE sleep offset difference group effects on BMI, HbA1c, sleep duration, systolic BP, diastolic BP, and physical activity.

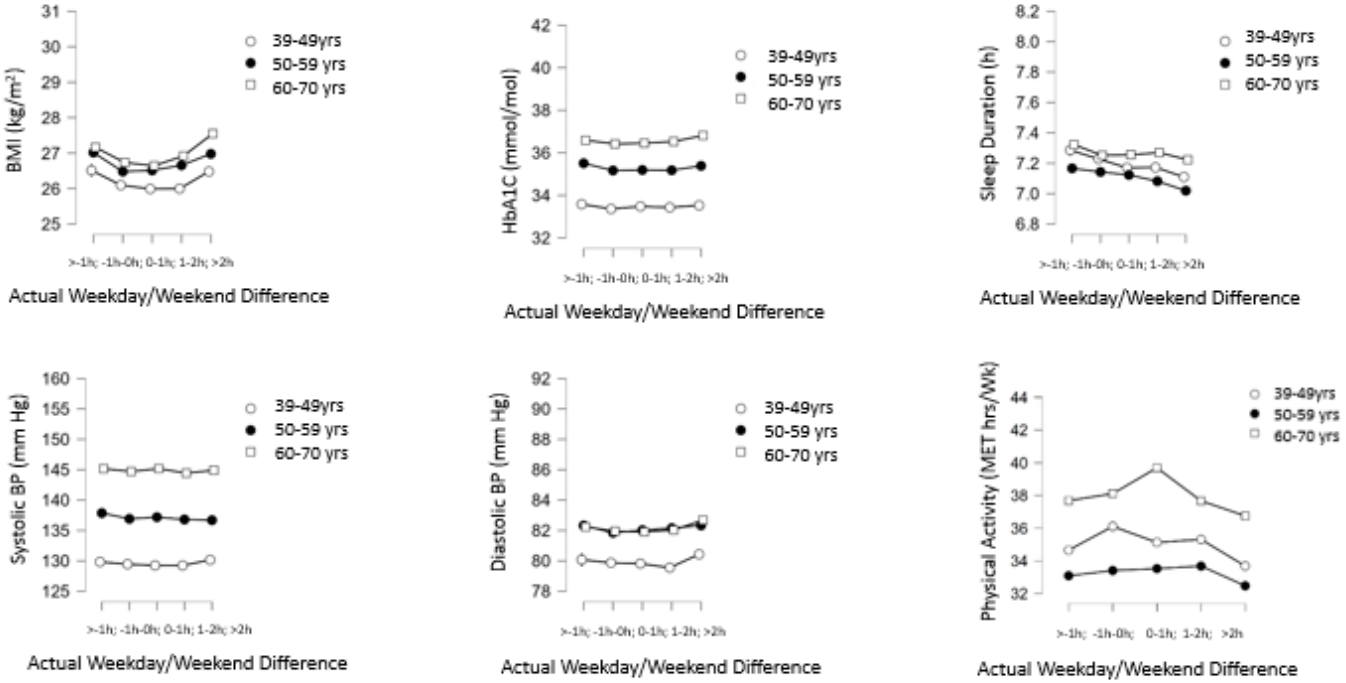
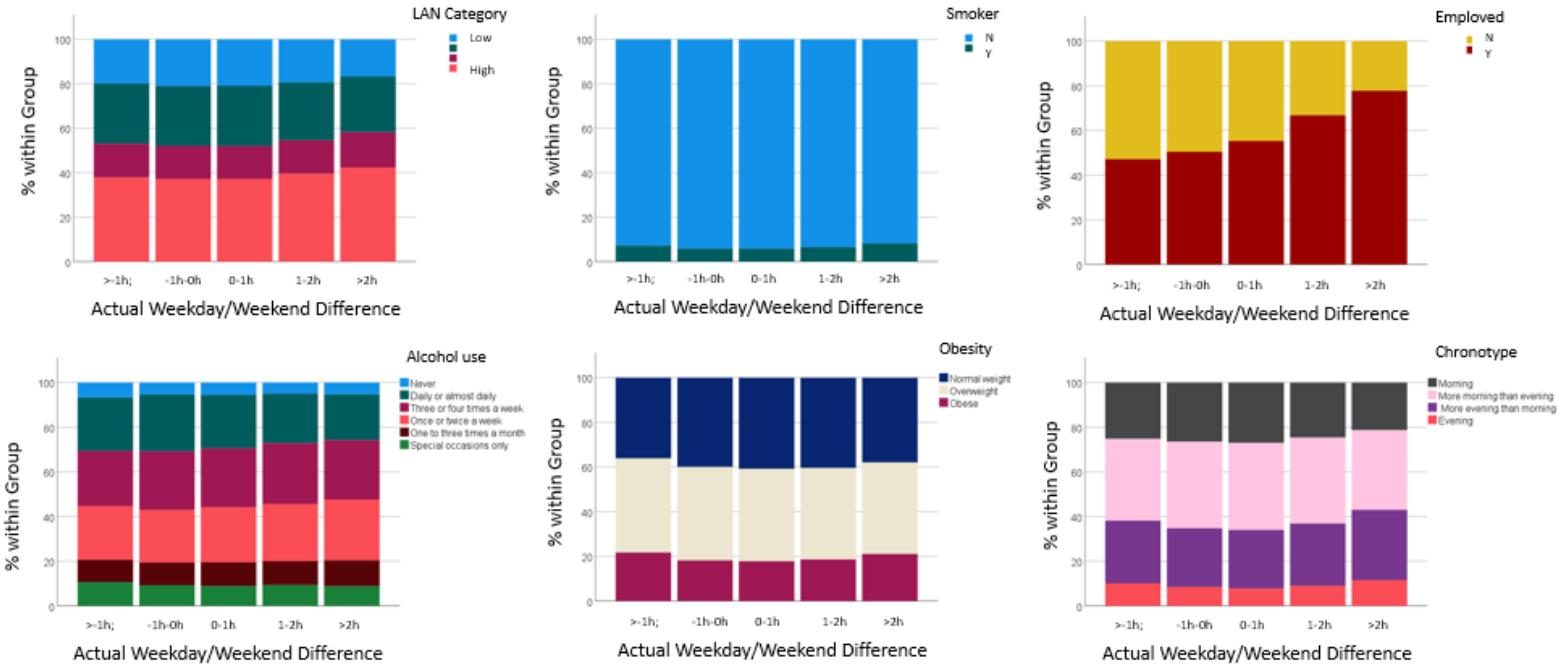


Figure 5.9

Bar plots illustrating the relationships between actual WD/WE sleep offset difference groups and LAN grouping, smoker status, employment status, alcohol use, obesity group and chronotype.



5.3.4 Predictors of WD/WE Sleep Offset Difference

In order to examine the relative associations of demographic, sleep and cardiometabolic factors with WD/WE sleep offset differences, we undertook hierarchical multiple regression with absolute WD/WE sleep offset difference as the dependent variable and the sequential additional of blocks of predictor variables (age and sex in step 1, Townsend deprivation score, LAN (highest/other), smoker (yes/no) and work status (employed/not employed) in step 2, sleep duration and chronotype (morning/evening) in step 3 and BMI, HbA1c, physical activity, systolic BP and diastolic BP in step 4; Table 5.5). For the complete model in step 4, the R^2 was 0.052, with age, sex, deprivation, LAN, smoking status, work status, chronotype, BMI and physical activity being significant predictors. Age had the largest beta value (-0.179), then employment status ($\beta = 0.050$), followed by BMI ($\beta = 0.041$) and then chronotype ($\beta = 0.041$).

Table 5.5

Hierarchical multiple linear regression models with absolute WD/WE sleep offset difference as the dependent variable.

	R^2	R^2 Change	β	B	SE	CI 95% (B)
Step 1	.045***					
Age			-.212***	-.023	.000	-.024 / -.022
Sex			.035***	.060	.007	.047 / .073
Step 2	.048***	.003***				
Age			-.181***	-.019	.001	-.020 / -.018
Sex			.032***	.054	.007	.041 / .067
Deprivation			.025***	.008	.001	.005 / .010
LAN			.011*	.019	.008	.004 / .034
Smoker			.018***	.063	.014	.036 / .089
Work Status			.050***	.085	.008	.069 / .101
Step 3	.050***	.002***				
Age			-.177***	-.019	.001	-.020 / -.018
Sex			.031***	.053	.007	.040 / .066
Deprivation			.024***	.007	.001	.005 / .010
LAN			.010*	.017	.008	.003 / .032
Smoker			.016***	.053	.014	.026 / .080
Work Status			.051***	.086	.008	.070 / .102
Sleep Duration			-.005	-.004	.003	-.011 / .003
Chronotype			.043***	.074	.007	.061 / .088
Step 4	.052***	.002**				
Age			-.179***	-.019	.001	-.020 / -.018
Sex			.028***	.047	.007	.033 / .060
Deprivation			.021***	.006	.001	.004 / .009
LAN			.011*	.018	.008	.003 / .033
Smoker			.016***	.053	.014	.026 /.080
Work Status			.050***	.085	.008	.069 /.101
Sleep Duration			-.003	-.003	.003	-.010 / .004
Chronotype			. 041***	.071	.007	.057 / .084
BMI			.041***	.008	.001	.006 / .009
HbA1c			.005	.001	.001	-.000 / .002
Physical Activity			-.008*	-.000	.000	-.000 / -.000
SBP			-.004	-.000	.000	-.001 / .000
DBP			.001	.000	.000	-.001 / .001

Note. β = standardized beta value; B = unstandardized beta value; SE = Standard errors of B; CI 95% (B) = 95% confidence interval for B; N=60,710; Statistical significance: *p < .05; **p < .01; ***p < .001. LAN = high light at night vs low; Chronotype =Morning vs evening; SBP=systolic blood pressure; DBP=diastolic blood pressure.

5.3.5 Weekday-Weekend Day Differences in People with DM

Those who were identified as having diabetes were then investigated. Of our sample with good actigraphy and measures of HbA1c the total number of participants with diabetes was 2522. HbA1c was investigated in these and anyone who's HbA1c fell below the prediabetes range (< 42; N = 585) were excluded. This analysis was therefore conducted in 1937 participants who had HbA1c ≥ 42 and were classed as having a diagnosis of diabetes. Actual weekday-weekend differences were investigated first, and no significant associations were found with BMI, physical activity, HbA1c or systolic BP. A very small positive association with diastolic BP was identified (r = .07, p = .005). Regarding absolute weekday-weekend differences there was a very weak positive association with BMI (r = .06, p = .013) and a weak negative association with physical activity (r = - .06, p = .009) and systolic BP (r = -.05, p = .047), but no significant association with HbA1c or diastolic BP were identified. See Table 5.6 for more details.

Table 5.6

Correlations between actual weekday-weekend day sleep offset differences and the measures of cardiometabolic health in particpants with diabetes.

Variables	1	2	3	4	5	6	7
1. Absolute WD/WE difference	1						
2. Actual WD/WE difference	.484***	1					
3. BMI	.056**	.033	1				
5. Physical Activity	-.060**	-.033	-.174***	1			
6. HbA1c	.023	.018	.015	-.002	1		
7. SBP	-.046*	-.007	.071**	.000	-.001	1	
8. DBP	.045	.066**	.222***	-.010	.053*	.508***	1

Note. N = 1937 for all variables except physical activity (PA; N = 1905), SBP/ DBP (N = 1842). Associations involving these 3 variables therefore have a smaller sample size. PA and absolute/actual misalignment = 1905; SBP/DBP and all variables except PA = 1842; PA and SBP/SBP = 1812.

5.4 Discussion

This study investigated actual and absolute weekday-weekend day sleep offset differences in a large dataset using the UK Biobank. This provided a measure of sleep timing misalignment which captured the tendency of participants to either delay or advance their sleep timing at the weekend in comparison to during the week. This served as a proxy measurement of SJL. A recent longitudinal study used differences in sleep offset timing between week and weekend days as one of their measures of circadian misalignment as it offered a measure that participants have practical control over (Jonasdottir et al., 2021). In our sample there was an average delay of just over 30 minutes, described as the actual weekday-weekend day sleep offset differences above. In absolute terms the change or mismatch in sleep timing across the week was larger, averaging around one hour. The distribution of the actual weekday-weekend day sleep offset differences was less skewed than the absolute weekday-weekend day sleep offset differences which aligns with previous research on SJL (Roenneberg et al., 2019).

There are currently few descriptions of negative SJL because most studies assess the effect of absolute SJL on health making estimates regarding negative SJL difficult (Kohyama, 2017; Roenneberg et al., 2012). A large proportion of this sample displayed negative weekday-weekend day sleep offset differences, or in other words an advance in sleep offset timing at the weekend (31.7%). This is higher than previous studies assessing midsleep differences; 14.3% in a study of 21–35-year-olds conducted by McMahon et al. (2018), 6% of the overall population in Komada et al. (2019) and only 1.7% in Roenneberg et al. (2019). This suggests potential difference in looking at sleep offset instead of midsleep. It is possible that some individuals may have been working on weekend days and may have woken up earlier on these days as a result. However, the potential impact of this should have been minimised by the exclusion of shift workers and unrealistic weekday-weekend day sleep offset values outside of three standard deviations. Previous research by Hashizaki et al. (2015) noted 26-minute delay in bedtime, and a 53-minute delay in wake time between weekdays and weekend days. Our study found a slightly smaller delay in sleep offset timing (wake timing) of 34-minutes, however Hashizaki et al. (2015) examined data collected from a contactless biomotion sensor which has a tendency to exaggerate wake time which may explain the differences. This misalignment or difference in sleep offset

timing suggests that social obligations and work may be restricting, or disturbing peoples sleep patterns.

In this sample males had greater absolute and actual weekday to weekend day sleep offset differences, although the effect size was very small. Research on gender differences regarding weekday-weekend day sleep onset/offset differences and SJL has been mixed (Caliandro et al., 2021) and Jonasdottir et al., (2021) did not describe any notable trends in either males or females. Some research suggests that males might have more SJL in early adulthood but that this might plateau in middle adulthood which is also associated with an advancing chronotype (Roenneberg et al., 2012). Decreasing weekday-weekend day sleep offset differences, both actual and absolute was associated with increasing age, which was in line with previous research suggesting that younger individuals display more weekday-weekend day differences and SJL than older individuals (Hashizaki et al., 2015; Jonasdottir et al., 2021; Wittmann et al., 2006). The reason for this is likely multifaceted and not fully understood. This may partially be due to the fact that as age increases, peoples chronotypes tend to advance and evening chronotypes are known to be at increased risk for displaying more SJL (Wittmann et al., 2006). Older individuals can still display some SJL or weekday-weekend day differences in sleep timing but usually to a lesser degree (Garefelt et al., 2021; Jonasdottir et al., 2021).

Work status differences in weekday-weekend day sleep offset differences were also expected, and those working either full time or part time displayed more actual and absolute sleep offset differences than those not working. This is likely due to those unemployed not having the same social restrictions during the week as those in full time work. Importantly, those not working still displayed some weekday to weekend day sleep offset differences. Some recent research has shown among recently retired individuals that SJL is still present but decreases significantly from that shown six months prior to retirement (Garefelt et al., 2021). Jonasdottir and colleagues (2021) also found weekday-weekend differences in sleeping patterns in older adults suggesting that we cannot assume that older adults will have standard week/weekend day schedules. We also identified that both actual and absolute weekday-weekend day sleep offset differences decreased with increasing age in those who were working and not working. This highlights also that age-related decrease in weekday to weekend day sleep offset differences was not purely due to greater proportions of older participants

retiring. Garefelt et al. (2021) suggests that social activities and having a bed partner in full time employment may drive this weekly misalignment which may explain some of the weekday-weekend sleep offset differences in our sample. Furthermore, age related changes in chronotype may also contribute to this with those with a later chronotype, even if older, displaying more week-weekend sleep offset differences.

In this study those who were the most deprived and exposed to the highest levels of artificial LAN also reported greater absolute and actual weekday to weekend day differences in sleep offset timing. It is well established that light in the evening acts to delay the circadian clock (Duffy & Wright, 2005) and it may be through this delay that higher LAN results in greater actual and absolute weekday to weekend sleep offset differences. Socioeconomic status (SES) is an important predictor of health and those in the lowest quintile of the Townsend deprivation index capture those with the lowest SES. Greater deprivation being associated with greater weekday to weekend day differences in sleep timing was not surprising. However, some previous research has actually found lower SJL in those in the lowest income quintile (Forbush et al., 2017). Smokers also demonstrated more actual and absolute week to weekend day differences in sleep offset timing. Previous research on SJL also identified a link between greater SJL and smoking status (Wittmann et al., 2006). As expected, those with a later chronotype had greater absolute and actual weekday to weekend day sleep offset differences. However, the effect size was very small. Those with a later chronotype tend to display greater misalignment because their internal biological clock does not match the external social schedule that modern society promotes through early work start time for example (Roenneberg et al., 2012; Wittmann et al., 2006).

A considerable amount of previous research looking at the impact of SJL on health focuses on the absolute value, however, the potential role of negative SJL is relatively unknown (Roenneberg et al., 2012). This study investigated the differences between some metabolic variables among the five groups of weekday to weekend day differences ranging from more than 1-hour negative misalignment to more than 2 hours positive misalignment. Participants showing more than 2 hours positive weekly sleep offset differences were significantly younger, and many health variables including glycated haemoglobin and blood pressure are impacted by age. This led to the stratification of the sample by age. Subsequent analysis found no differences in

HbA1c levels between the five groups, this was not unexpected as only a very small percentage of the sample had a diagnosis of diabetes. Systolic BP did not show any differences across misalignment groups in any age category. Diastolic BP did not vary systematically. In the youngest group having more than 2 hours weekday to weekend day sleep offset differential was associated with higher blood pressure than with 1-2 hours sleep offset differential. No differences were found in the middle age group. In the oldest group those with more than 2 hours weekday to weekend day sleep offset differential had higher diastolic BP than those with between negative 1 hour and positive 1 hour sleep offset difference. Previous research among healthy young adults did not find an association between SJL and blood pressure (McMahon et al., 2019). Further, Rutters et al. (2014) failed to find any differences between SJL groups in terms of either systolic BP or diastolic BP, however they had no negative misalignment group. The findings for systolic BP are therefore consistent with previous research though the reason for the slight differences in diastolic BP is unclear.

Interestingly, irrespective of age those with the most positive and negative weekday to weekend sleep offset differences tended to have a higher BMI although the significance of these groupwise differences varied between age groups. The differences are very small but in line with some previous studies which have reported an association between greater SJL and greater BMI (Parsons et al., 2015; Roenneberg et al., 2012). However, some research has failed to find a difference in BMI between groups of SJL (Rutters et al., 2014). This was significantly smaller and no major difference in the effect of positive and negative weekday-weekend day sleep offset differences suggests that maybe they have the same negative effect on health, as debated by a recent systematic review (Henderson et al., 2019). In terms of behavioural variables unlike some previous research which found that those with the most SJL self-reported lower levels of physical activity (Rutters et al., 2014), no differences in physical activity were found in those aged 39-49 or 50-59. Interestingly, among those aged between 60-70 those with 0-1 hours of weekday-weekend day sleep offset differences showed the highest physical activity levels in comparison to all other groups.

Linear regression demonstrated that younger age, being male, greater deprivation, greater LAN, working, evening chronotype, greater BMI and lower physical activity were significant predictors of absolute weekday to weekend day

differences in sleep offset timing when controlling for additional sleep, demographic, and behavioural variables. These explained 5.2% of the variance with younger age being the strongest predictor. This adds an additional layer to the association between certain demographic, behavioural and cardiometabolic variables and week to weekend sleep offset differences.

In a subgroup of participants with diabetes and HbA1c of 42 mmol/mol and above no strong associations between either actual or absolute weekday-weekend day sleep offset differences and various cardiometabolic variables were observed. There was a very small association between greater absolute weekday-weekends sleep offset differences and BMI, which was not unexpected as misaligned sleep timing has been associated with obesity in the past (Roenneberg et al., 2013). Unlike chapter 2, we found no association between this measure of either actual or absolute weekday-weekend day sleep offset differences and HbA1c. This suggests that week to weekend day sleep offset differences may not influence HbA1c. However, there was a period of time between the collection of blood samples for HbA1c and the wearing of activity monitors and sleep timing may have changed between these time points. Furthermore, it is important to remember that there is a difference in SJL and our conceptualisation of weekday-weekend day sleep offset timing.

5.4.1 Strengths and Limitations

Although this study allowed for the objective analysis and calculation of differences in sleep timing across the week, allowing the objective quantification of wake time delays and advances there are some limitations that warrant discussion. At the time of analysis, no information on sleep onset was available and our measure of weekday-weekend day sleep timing is a distinct concept to SJL because it did not use the formula originally suggested by Wittman et al. (2006). However, a similar measure has been used in analysis conducted by Jonasdottir et al. (2021). Further, although shift workers and unrealistic values were excluded, no information on work and free days were available and as such it is not known whether or not people may have been working at the weekend and may have shifted their sleep offset earlier as a result. It is likely that a small proportion of our sample fell into this group whereby they may have been working in sales and services for example. Nonetheless this calculation does offer some valuable information on how people may shift their sleep timing over the week

and has been used by several other researchers (Hashizaki et al., 2015; Jonasdottir et al., 2021; Kuula et al., 2019). Another limitation is that a period of time passed between obtaining the baseline measures (2006-2010) and the collection of the activity data (2013-2016) and these may not map perfectly onto each other as a result.

Working with large datasets brings distinct strengths and limitations. The main strength is the power obtained, which can be difficult to achieve in other studies. However, with increasing sample size the phenotyping often decreases, and less detailed information is gathered. In this study gathering weekday-weekend day differences and chronotype in over 70 thousand participants offered the ability to visualise these variables in a very large number of participants. However, only one single question assessed chronotype and there was only one week of activity data gathered. This limits the conclusions that can be made about human behaviour. Furthermore, statistical significance does not always equal psychological significance. Relationships and differences observed while statistically significant may not be clinically or psychologically important.

5.4.2 Conclusion

In summary, sleep and circadian misalignment have a high prevalence in society. This study noted a high percentage of both negative and positive weekday to weekend day sleep offset differences and a description of these in a large database. Actual weekday-weekend day sleep offset differences showed a less skewed distribution than absolute weekday-weekend day sleep offset differences. As expected, both measures decreased with age and those with the late chronotype showed the greatest weekday-weekend day sleep offset differences. Presumably due to the constraints of a work schedule those working experienced more absolute and actual weekday-weekend day sleep offset differences, however participants not working still experienced this weekday to weekend day differences in sleep offset timing. This suggests that people may experience this for their entire lives rather than just their working careers. Interestingly, weekday-weekend day sleep offset differences decreased with age in those employed and not working. The drivers are likely to be different and are not fully understood. Those with the most positive misalignment were significantly younger and when the sample was stratified for age

no large effects were found in terms of differences of our health-related variables between groups.

Chapter 6:

A Qualitative Study on Factors Influencing Sleep Timing and Daily Routines in Retired/Non-Working Adults with T2D.

Abstract

SJL, the behavioural manifestation of circadian misalignment persists all throughout the working years and after retirement, albeit to a lesser degree. The aim of this current study was to determine how much sleep varies among a non-working group of individuals with T2D and what factors drive this sleep and daily routines more generally. Seventeen semi-structured interviews were conducted among individuals with T2D who were retired (N = 11) or not working at the time of the interview (N = 6) and data were analysed using reflexive thematic analysis. Four main themes were generated: "consistent sleeping patterns" characterised by habit or routine, age and retirement reduced influences, ownership over the environment before bed and unavoidable morning curtailments; "fluctuating sleeping patterns" characterised by quality of TV, maintaining a sense of normality and derived social zeitgebers from household members; "night-time disruptions" characterised by rumination, nocturia and secondary complications; and "lasting effort needed with T2D diagnosis" characterised by the burden of the disease, lifestyle and dietary changes and active role played in learning about the disease. All of this data provided some rich and nuanced information on what can lead to consistent sleeping patterns, and what can lead to fluctuating patterns preventing more synchrony between schedules across the week. This information may be adapted to help develop interventions for individuals with fluctuating patterns due to things like television viewing. Many participants experienced frequent night-time disruptions, and this should be considered as something that might influence sleep timing beyond sleep quality. Further, a lasting effort was identified with the diagnosis, and it may be the case that a diagnosis of diabetes brings many lifestyle changes that can be difficult to manage at times. For this reason, all interventions should be easily accessible, and easily implemented to prevent additional stressors on participants.

Keywords: Reflexive thematic analysis, type 2 diabetes, consistent sleeping schedules, fluctuating sleeping schedules, night-time disruptions.

6.1 Introduction

Timing of sleep, in addition to some of the more common sleep variables such as sleep duration and sleep quality is increasingly being recognised as an important factor for good health. As previously described in chapter 1, SJL has been associated with numerous health issues ranging from increased unhealthy lifestyle behaviours to obesity and diabetes (Koopman et al., 2017; Parsons et al., 2015; Roenneberg et al., 2012; Wittmann et al., 2006; Wong et al., 2015). When Wittmann et al. (2006) initially described SJL it was conceptualised as something that only impacts people during their working life. This view has continued with a lot of research focusing on these cohorts. However, recent research has shown that people still display SJL, albeit to a lesser degree after retirement (Garefelt et al., 2021; Sprecher et al., 2020). The reasons for this SJL in retirement are unclear as the same work constraints do not exist. However, it is important to note that social zeitgebers including social interaction and relationships with people have the ability to influence circadian rhythms (Zaki et al., 2020). Garefelt and colleagues (2021) suggested that some *"social zeitgebers"* can impact sleep timing among a retired cohort. These *"social zeitgebers"* may include social activities and television viewing for example. Garefelt et al. (2021) also discussed the concept of *"derived social zeitgebers"* whereby the schedule of an individual's partner may also be playing a role. All of this highlights how a social perspective needs to be considered when thinking about sleep as it is not simply an individual phenomenon.

SJL is very prevalent and tends to decrease with age. Sprecher and colleagues (2020) identified that SJL decreased by around one hour when moving from full-time employment to full time retirement. Furthermore, in this study, those with greater SJL reported poorer self-reported health (Sprecher et al., 2020). Garefelt et al. (2021) observed a 40-minute decrease in SJL after retirement. In this research those with a later chronotype had larger SJL changes and those with a partner in full time employment had smaller SJL changes. Altering sleep timing or reducing SJL can be difficult due to societally imposed schedules. There are two potential approaches, one option could be to advance the internal circadian clock so there is no major discrepancy between a week and a weekend day. The second option might involve the removal of social constraints that curtail sleep timing.

Zerbini and colleagues (2020) attempted to modify the light environment and advance the internal circadian clock so that an individual would then have a greater chance of matching the external schedule. Reducing evening light exposure advanced sleep timing and melatonin after one week but no change in SJL was observed (Zerbini et al., 2020). Furthermore, this was not evident after two weeks. Morning light exposure did not change any of these parameters. This suggests that altering light environments may help individuals to cope with early work schedules but producing long-lasting effects is difficult. In retired individuals these societal schedules do not exist to the same extent, and it may be more feasible to alter sleep timing with simple behavioural alterations. This could then have a positive impact on many health outcomes, including T2D management.

While Garefelt et al. (2021) discussed some social and derived social zeitgebers impacting sleep among a retired cohort, this was a quantitative study and so it was hard to get a full understanding of what factors influence sleep timing. Further it is hard to determine how modifiable these behaviours might be. Qualitative research provides a more in-depth view of the experiences of participants (Braun & Clarke, 2006). One previous study looked at what influences sleep and meal timing through a qualitative lens and identified many factors including the environment, SJL, and busy schedules (Goheer et al., 2021). However, this was in a group of people mainly working and therefore with somewhat fixed social constraints. Understanding what drives sleep and wake in a retired/not working cohort, especially with a chronic metabolic disease could offer new insights. Previous research has shown for example that individuals with diabetes report that timing of food is impacted by medication (Lee et al., 2016). The impact this could have on sleep/wake times is unknown.

The overall aim of this study was to investigate to what extent social factors impact sleep timing among retired individuals or individuals who were not currently working with T2D through a qualitative lens. Qualitative research has the ability to provide rich, nuanced, and in-depth detail that cannot be obtained from quantitative research alone. The use of qualitative research in sleep science has been limited to date but by investigating peoples lived experiences we can hopefully guide future policy and inform clinicians. This study had a number of research questions to achieve this aim.

1. Do “social zeitgebers” impact sleep timing in this cohort?
2. What are the timing constraints (“social zeitgebers”) that lead to SJL? Or what leads individuals to keep a consistent schedule across the week?
3. Are there any modifiable behaviours that commonly appear among those with SJL that may be altered or are there any behaviours that consistent sleepers display that may be adapted to improve alignment between sleep time on week and weekend days?

6.2 Methods

6.2.1 Study Design

We conducted a qualitative analysis whereby all participants completed a one-to-one semi-structured interview, and an inductive thematic approach was used for analysis. Demographic details including age, sex, employment status (retired or not currently working), employment status of partner, diabetes duration, household size, medication use, and insulin use were also obtained from participants. Gathering this involved some participants completing a short survey prior to the interview (N = 6) while others provided these details at the beginning of the interview (N = 11). Demographic questions answered by all participants can be viewed in Table 6.1.

Table 6.1

Structured demographic questions asked at beginning of interview for those who did not complete the initial survey.

Demographic questions 1. What age are you? 2. What is your gender? 3. How long have you had type 2 diabetes? 4. Are you retired? If yes, for how long? 5. Are you unemployed? If yes, for how long 6. Are you a smoker? 7. How many people in your household? 8. What is your marital status? 9. Do you have a bed partner and if yes do they work full time?
Diabetes management 1. On a scale of 1-10, 1 being very poor and 10 being excellent how would you rate your management of type 2 diabetes? 2. Are you currently taking any glucose lowering medication? 3. Do you use insulin? 4. Do you have any diabetes related health consequences?

6.2.2 Participants

This sample was acquired using a convenience sampling method. The inclusion criteria for this study were that people were 40 years or older, had a diagnosis of T2D and were either retired or not working at the time of the interview. The study

was advertised online through Diabetes Ireland and Diabetes UK. The study was also shared online using social media platforms such as Twitter and Facebook. Specific T2D support groups were approached and flyers for the study were shared with some diabetes clinics to reach further participants. Beyond this participants were recruited through word of mouth. There was no incentive for participation. Ethical approval was obtained from the Maynooth University Social Research Ethics Subcommittee (SRESC) before commencing the study. Participants were numbered (Participant1, Participant 2 and so on) depending on when they participated. Names of specific locations and people were redacted from interview transcripts to ensure data were not identifiable in any way.

6.2.3 Data Collection

Data were collected through semi-structured interviews, conducted between April and September 2021. The interviews were informed by a schedule focusing on the reasons for sleep timing choices across the week. The associated meal timing choices and typical activities on a daily basis were also discussed (see Table 6.2 for interview schedule). The interviews were designed to encourage participants to think about and share what factors influence their sleeping patterns across the week. A series of overarching questions were developed with a number of prompts to encourage people to provide more detail. The questions were developed based on gaps in previous quantitative studies. The number of questions was important in order to fully evaluate these gaps in the previous literature. All prompts were not used with every participant, some participants naturally shared more information, while others needed additional prompting. The interviews lasted between 18 and 33.48 minutes (M = 24.27 minutes). Due to the restrictions imposed by the COVID-19 pandemic all interviews took place either online via Microsoft teams or over the phone depending on the participants preference and access to technology. The interviews were transcribed to produce an orthographic transcript whereby a verbatim script was developed that included all verbal and non-verbal utterances.

Table 6.2

Interview schedule of main questions and potential probes.

1. **What time you usually wake during the week and what influences this wake time Monday to Friday? *Can you tell me a little more about this?***
   Potential probes: *(these may vary depending on response to initial structured questions)*
   a. *Are all the weekdays the same or do they vary? Can you say a little more about this?*
   b. *How hard do you find it to wake at this time? Do you always get up straight after waking?*
   c. *Do you use an alarm to wake, or do you wake naturally? Does your partner use an alarm?*
   d. *Do you use insulin or any glucose lowering medication in the morning? If yes, around when and does taking your medication ever influence your wake time? i.e., would you need to set an alarm*

2. **Talk me through a typical weekday day. What activities do you do during the day and when?**
   Potential probes:
   a. *Do you engage in physical activity? Can you tell me a little more about this and the factors that influence the amount and timing of your physical activity?*
   b. *Do you spend long outdoors? What factors influence the amount and time you spend outdoors?*

3. **What time you usually go to bed on a weekday, so the nights preceding Monday to Friday and what factors affect what time you go to bed at?**
   Potential probes:
   a. *Are all the weeknights the same or do they vary? Can you say a little more about this?*
   b. *Do you try to fall asleep straight away? Does it take you long to fall asleep ?*

4. **Would you say you can freely choose your sleep and wake timing on a weekday?** Can you say a little more about this? Are there any *influences like children/ pets/ grandchildren/ hobbies?*

5. **What time do you normally wake on Saturday and Sunday, and what factors influences this?**
   Potential probes:
   a. ***Are both days the same? Please explain how and why they differ.***
   b. ***Does this occur naturally?*** *Alarm clock?*
   c. *How hard do you find it to wake?*
   d. *How long after waking do you rise?*

6. **Could you please talk me through a typical weekend day? What activities do you do during the day and when?**
   Potential probes:
   a. *Do you engage in physical activity? Can you talk to me about some of the factors which influence the amount and timing of your physical activity? Please detail any differences in comparison to the weekdays in terms of timing and amount.*
   b. *Do you spend long outdoors? What factors influence the amount and time you spend outdoors? Does your time outdoors differ between these week and weekend days?*
   c. *What time do you have to take medication at on weekend days? Does this have any impact on your sleep/wake or schedule?*

7. **What time do you go to bed at the weekends so Friday night and Saturday night, what factors affect what time you go to bed at?**
   Potential follow up questions:
   a. *Are both nights the same?*
   b. *Do you try to fall asleep straight away?*
   c. *Does it take you long to fall asleep? Any different to weekdays?*

8. **Would you say you can freely choose your sleep and wake timing on a weekend day?** Can you say a little more about this? Are there any *influences like children/ pets/ grandchildren/ hobbies?*

9. **V1:** Talk to me a little bit about how your sleep onset and end are slightly later/earlier at the weekend is there any reason for this? (i.e., do you prefer staying up later or getting up later?)
   a. *Are these curtailments important or unavoidable? Would you be able to keep a consistent schedule across the week? Would you be willing to modify them if it could have a positive influence on your health?*

   V2: Reflecting on your sleep timing behaviours, it seems that you sleep and wake pretty consistently across the week, are there any other factors not discussed above which might influence this?
   b. Do you make a conscious decision to keep this consistency across the week?

10. **Is there anything else you would like to add about your week and weekend day sleep timing?**

11. **Would you often nap during the week or at the weekend?**

12. **Have you ever tried monitoring or changing your sleeping habits to lose weight or improve your health or for other reasons?**

13. **Have you ever spoken to your GP/Consultant about your sleep timing or your sleep in general?**

14. **Do you have any stressors in your life currently that have impacted your sleep timing or sleep in general?**

15. **In general, would you describe yourself as more of a morning lark or night owl?**

16. **Do you typically eat breakfast? Can you tell me what time you eat this at, and does it vary between week and weekend days?**

17. **What do you typically eat for breakfast and does this vary between week and weekend days?**

18. **Can you tell me a little bit about the timing and content of your other meals on a typical day?**
    Potential probes:
    a. *When do you eat your other meals throughout the day? What factors affect the content and timing of your meals? -> Does the timing or content of your food differ across the week – from weekdays to weekend days?*
    b. *Does this vary across the week? Does your medication or insulin use drive this?*

19. **Have you ever tried changing your food timing or habits in general to lose weight, improve health or for any other reasons?** *Please tell me more about this …*

20. Has any of this changed with the COVID-19 pandemic? Potential probes: a. *sleep timing/ food timing/ physical activity/ stress*
21. Is there anything else you would like me to know?

6.2.4 Data Analysis Procedure

Reflexive thematic analysis was used to analyse the data; this involved following the six steps outlined by Braun and Clarke (2006), but crucially also taking into consideration updates and advice published since then (Braun & Clarke, 2019). The steps involved in this process are outlined below but one of the key changes since 2006 is the emphasis on this thematic analysis being reflexive approach. This technique acknowledges the active role that the researcher plays in the theme generation process and this technique was chosen as it allows data driven analysis of the text and is theoretically flexible. For this reason, reflexive TA allows the investigation of people's views and day to day experiences which is useful for looking at what influences daily sleeping and waking patterns. For the coding and analysis, the researchers used a more inductive framework with semantic level coding where the focus on meaning was grounded in the data and the explicit things that participants said. The qualitative research software MAX-QDA was used to facilitate the familiarisation and coding of the data as well as the generation and review of themes. This software was also used to help compile quotes that supported the themes.

RK conducted the interviews, transcription, and analysis of the data. The first step as outlined by Braun and Clarke (2006) involved familiarisation with the data. RK collected all of the data but also immersed herself in the data by transcribing all of the interviews. Once all of the interviews had been transcribed and checked for accuracy, they were imported into the MAXQDA software to aid the thematic analysis. RK then read and reread all of the transcripts. During this stage initial notes regarding the data were taken down. Step 2 involved coding the data, and codes identified were mainly semantic in nature rather than latent. The analysis is descriptive and summative where the participants were given a voice. The interpretation of meaning is therefore not central, but it is important to note that interpretation will always play a part in thematic analysis and there is value to this. MAX-QDA was used to create initial codes based on all of the interviews. This allowed codes to be easily

revisited. After the initial codes were developed step 3 involved themes being generated from recurring codes; the creative coding function on MAX-QDA was very useful for this purpose as it allowed the researcher to visualise and organise codes. Braun and Clarke (2006) initially described this step as *'searching for themes'* but in recent years prefer the phrase *'generating initial themes'* to match how their thinking around the themes has evolved. Searching for themes suggests that the themes are sitting in the data waiting to be found, whereas the generation of themes acknowledges the role that the researcher plays in this process (Braun & Clarke, 2019). This was an important part of theme generation. After the initial list of themes were identified they were reviewed and refined by the researcher (RK) until the coded extracts were adequately captured by the themes (step 4). After the initial themes were generated MAX-QDA was very useful for checking the accuracy of themes as it grouped all coded extracts together and it also provided a systematic way of making sure the entire dataset were coded for these themes. The final themes were then defined and named in order to allow accurate explanation (step 5). Our final themes were visualised using the creative coding function and figures were developed from here. The final step was to analyse and write-up the report and explain how the chosen themes were relevant to the data and the research questions (step 6). Notably, this method of thematic analysis is not a linear process, the stages had to be revisited several times to make sure themes were accurate and results were as reflective of the data as possible. Discussions were held between RK and her supervisor AC over the initial codes and the final themes. This was not simply to develop consensus but rather to ensure a rich and nuanced reading of the data. This ensured that RK's assumptions did not lead her to miss potentially important points and meanings within the data. The researchers do acknowledge their involvement of the field and the potential influence this may have had.

6.3 Results

6.3.1 Participant Characteristics

Seventeen participants with T2D were recruited as part of this study. Recruitment ceased after 17 participants as initial analysis suggested that the data was high in information power. This judgement was based on Maltreud et al. (2016)'s guidelines. Demographic details of the participants can be viewed in Table 6.3. The mean age was 64.18 (*SD* = 8.19) and ranged from 48 – 77 years. Nine participants were female (52.9%), 11 participants were retired (64.7%), while 6 participants were not working at the time of the interview (35.3%).

Table 6.3

Descriptive characteristics of the sample.

Participant	Age	Gender	Work Status	Duration of T2D	Smoker	Household size	Medication	Insulin	MSFsc	SJL
1	60	M	Retired	9 months	No	2	Yes	No	4:37	0:45
2	55	M	Currently not working	1 year 11 months	No	3	Yes	No	3:43	0:23
3	70	F	Retired	4 years 8 months	No	1	No	No	4:05	0:00
4	65	M	Retired	11 years 6 months	No	5	No	No	2:40	0:00
5	63	F	Retired	16 years	No	2	Yes	Yes	5:05	0:00
6	73	M	Retired	16 years	No	2	Yes	No	2:30	0:00
7	57	F	Currently not working	17 years	No	4	No	Yes	2:57	1:07
8	48	F	Currently not working	7 months	Yes	2	Yes	No	3:09	0:00
9	61	F	Currently not working	1 year	Yes	1	Yes	No	5:13	3:15
10	51	M	Currently not working	15 years	Yes	6	Yes	Yes	1:53	0:23
11	72	M	Retired	6 years	No	2	Yes	No	3:45	0:00
12	64	M	Currently not working	7 years	No	2	Yes	No	3:08	0:00
13	73	F	Retired	7 years	No	2	Yes	No	2:15	0:04
14	66	F	Retired	5 years	Yes	5	Yes	No	4:37	-0:23
15	77	F	Retired	10 years	No	3	Yes	No	3:34	0:00
16	65	M	Retired	16 years	No	5	Yes	No	3:30	0:00
17	70	M	Retired	22 years	No	2	Yes	Yes	3:15	0:00

6.3.2 Reflexive Thematic Analysis

From our semi-structured interviews four distinct themes were generated. The first two themes represent two groups of individuals with T2D; those who kept a consistent sleeping pattern across the week and those who described a fluctuating sleeping pattern. These themes had between three and four sub-themes detailed below. The third theme was "night-time disruptions" which has a potential impact on sleep timing and the fourth was "lasting effort needed with T2D diagnosis". Specific quotations are provided in italics in support of each theme and associated subthemes below.

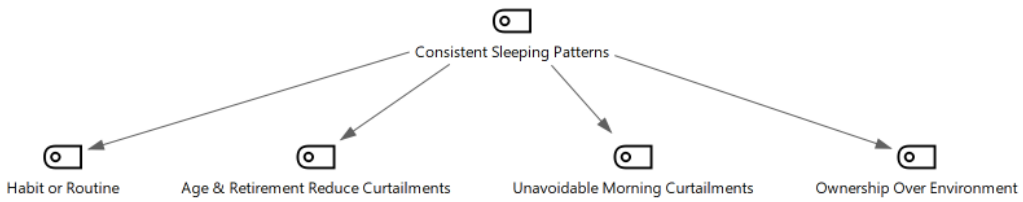
Theme 1: Consistent Sleeping Patterns

"Well, I sleep in and around the same time every night like." (Participant 13)

Many participants described a very consistent sleeping pattern where they went to bed around the same time every night and woke up around the same time every morning. The four subthemes which were generated explaining this were "habit or routine", "unavoidable morning curtailments", "retirement and increasing age induced similarities" and "ownership over environment before bed" (see Figure 6.1).

Figure 6.1

Thematic map of our first main theme consistent sleeping patterns and it's four subthemes: habit or routine that participants have developed; age and retirement reduced curtailments allowing participants to freely choose these patterns; unavoidable morning curtailments including requirements which get people up in the morning and may impose a level of consistency; and finally, ownership over potentially disrupting factors in the environment before bed.



Subtheme 1: Habit or Routine

"You get into a routine and you-you- if its working for you, you try and stay that way. That's the way it is." (Participant 6)

Some participants have developed a consistent daily routine of sleeping and waking and as suggested by participant 6 above, it may be that this particular routine allows them to function competently. While it is possible that people just fall into this pattern over time, it may also be that the people reporting consistent sleeping patterns have a natural tendency towards preferring to maintain a daily routine. Participant 17 described himself as a *"fairly routine sort of person, you know what I mean, same time everyday kind off"*. When participant 16 was asked to talk about any differences between a typical weekday or a weekend he stated, *"There's no difference, it's the same, every day is the same"*, while another participant remarked *"it's the exact same thing every day"* (Participant 12). It appeared as if these participants preferred to keep this organisation *"I like to be organised and up in bed by 12" … "even though I wouldn't have anything in particular to attend too I still like to have that getting up time"* (Participant 3). Participant 13 gets up consistently as she loves the early morning *"I love getting up in the mornings and I'm a good person for going to bed early at night. It's nine o'clock to bed for me."* She also described this as a natural automatic wake time.

> *Every day, I'm very, very organised in me own way, yeah. I wake at quarter to eight and I get up at eight o'clock, yeah.*
>
> *…*
>
> *I do wake naturally at that time, I'm used of it like. I wake at the same time yeah.* (Participant 13)

One participant even described this natural wake while on holidays.

> *I mean I am, you know we just went away last week for a few days, but am first time we've been away, just down to* [redacted] *and yeah it was funny like we were just saying that we woke up at exactly the same time even in the hotel. So, I suppose am we're just into that routine now, you know wakening up at around 7ish.* (Participant 15)

It may have been that certain people slept and woke more naturally throughout their lives and then transitioned naturally into having a very consistent sleeping pattern after retirement. For example, participant 4 described waking naturally for years.

> *Am yeah, I mean, let's be honest, I haven't set an alarm clock-, the only time I've ever set an alarm clock is we got am you know some transportation to catch, a plane or a, or a train, if we can remember back that far to when we could do those kinds of things.*

Subtheme 2: Unavoidable Morning Curtailments

Some necessary daily morning curtailments made it more likely for participants to maintain regular sleeping patterns. These participants often described waking naturally but needing to for a specific reason. One participant described having to wake to check her blood sugar levels *"just for a sort of safety reasons 9 o'clock, I wouldn't let it go much later than 9, ehh just to check my bloods."* (Participant 5). This participant did state that it was a natural wake time.

> *if I wasn't awake, I'd be almost awake, you know that kind of way.*
>
> *...*
>
> *So I suppose like my blood checkers and medication and that do dictate my time to a certain extent, but not it's not intrusive, it's not that I'd notice it as such.*

Participants also spoke about how pets can contribute to this consistent schedule. Participant 16 had to rise to care for his dogs *"I get up every morning we'll say around 7, and I'll go out, I have dogs, I let the dogs out".* Other participants reported being woken by the dog every morning.

> *I think the dog is the one that is more used to the trigger, so when the dog wakes up and wants to, you know, go downstairs and have its breakfast so on, that tends to make us realize it's time to get up, you know.* (Participant 4).

Light entering the room also seemed to be a factor that led to consistent wake times *"I think it's the bright, the brightness is what's waking me."* (Participant 3).

> *I suppose the only other thing is am, is daylight, am in that, yeah, I mean I suppose part of what governs when you get up is how light it is in the bedroom when you when you first come to.* (Participant 4).

Finally, it is also possible that the schedule of their retired partner may also influence wake time in the morning. While participant 6 noted that they *"work away together"* another participant described a situation where her husband's natural wake every morning guided her natural wake *"Ehh my husband tends to wake about 7:00, I might sleep a bit later, but he hah when he starts to move I kind of wake up"* (Participant 15)

Subtheme 3: Age and Retirement Reduce Curtailments

Some participants described how seven days of the week are similar in terms of activity and mentioned how older age and retirement reduced these changes. *"That's really most days, you know. When you retire the weekends don't matter as much as when you're not retired, you know, so that would kind of be seven days a week, yeah."* (Participant 15). Participant 5 similarly said:

> *Yeah, I mean, as I said normally the seven days of the week would be the same but just at this particular moment, we don't go out quite as much to avoid crowds we don't go out as much on the weekends anymore, but in the normal world all the days would really be more or less the same.*

Participant 4 commented on how this may actually be a challenge *"Amm there quite similar across the week now. Amm you know there's no, in fact one of the challenges I think when you pack up work is to try and make not every day the same haha."*. When asked about how sleep timing may differ at the weekend participant 13 responded *"It's the same, it's the same for me now, sure I'm seventy-three years of age sure what else would I be doing haha"* suggesting that with older age the curtailments are reduced, and this may lead to a more predictable schedule of sleep and wake.

Subtheme 4: Ownership over Environment

Some people with this routine around sleeping and waking described an awareness of how some factors impacted sleep. This included some reading a book for a certain amount of time *"I find it virtually impossible to go asleep unless I read for a while."* (Participant 15). Participant 15 went on to stress this:

> *I have to read, I mean I absolutely have to read. I remember we went to a hotel one time, and I forgot my book and and and and I read all the brochures. I literally have to read something before I go asleep.*

One participant noted turning the TV off at 10:30 due to the adrenaline in some shows *"We tend not to watch TV after about 10, 10:30 ish and ah at the moment we, we're watching prison break and there's a lot of adrenaline in that."*; similarly participant 5 reduces technology use in the hours before bed and *"would consider that a bad habit to turn on the laptop after 10 o'clock."*. Participant 3 looks at the newspaper and tablet during the day to avoid this at night.

> *I find that if I spend time on my tablet looking up emails or newspapers cause I get the newspapers online, that would keep me awake if I was on it before I go to bed. So, I have to make sure I'm not doing that, I try and get that done during the day. Amm because it became a habit that I just watched the tablet and listen to the news or look at the newspaper.*

While participant 15 also describes having no screen stimulation in the bedroom *"I don't have a television in my bedroom, and I don't ehm I I guess I have my phone but I put it in a drawer so I don't have that in the room."*. All of these positive behaviours are signs of good sleep hygiene and have influenced these participants showing a certain sleeping habit.

Theme 2: Fluctuating Sleep Timing

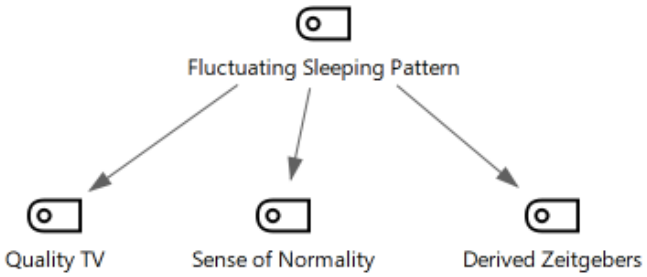
"*I don't know it just- I'm not really somebody who has, uhm, regular habits, so I just sort of go with the flow."*. (Participant 8)

Some participants reported varied sleep timing day to day and a flexibility around their sleep timing as they were not working. This might have been due to simple factors like getting up earlier some mornings to walk (participant 11) or just

relaxing for longer some evenings before bed (participant 9). Three subthemes were generated that to explain fluctuating sleeping patterns and these were: "Quality TV", "Maintaining a sense of normality", and "Derived zeitgebers" (see Figure 6.2).

Figure 6.2

Thematic map for our second overarching theme fluctuating sleeping patterns and it's three subthemes: Quality of TV programs, maintaining a sense of normality and distinguishing between the week and the weekend, and derived zeitgebers from the household's schedule.



Subtheme 1: Quality of TV

Daily variations in sleeping patterns were sometimes driven by very small things like the quality of TV programs available on a given night. If there is something 'good' on TV participants might stay up later but if there's nothing 'good' on, they might go to bed earlier.

> *Ehh, everynight, well it's different, it varies. I go maybe sometimes maybe half 11, more times maybe 12 / half 12 y'know half 11 half 12. Now there might be an odd night I might go late I might go d'ya know if there's something on it might be 1 o'clock/ half 1 but not always, its mostly around the 12ish, 11:30, 12 or it could be half 12.* (Participant 11)

When asked about the influencing factors TV programs seemed to be important *"Nothing in particular but you know I'd say well it's time to go now, wife's name might be gone before me you know. I just go because there's nothing much on TV and I-I'll go, you know."*. Participant 8 also described fluctuating sleeping patterns that were in

part influenced by what was on the television. Participant 8 also had a tendency to watch TV until she felt tired.

> *Uhm, depends how tired I'm starting to feel, depends on what I want to watch on TV, uhm depends on if I'm talking to my daughter, you know. I don't know it just- I'm not really somebody who has, uhm, regular habits, so I just sort of go with the flow.*
>
> …
>
> *well this is gonna be strange cause I kind of I go to my room and I watch TV for quite a while and I might try and fall asleep about half 10. Amm but if I can't get sleep I'll watch TV again.*

Participant 9 had a similar experience *"Amm aa I'm never in bed before eleven Rachael unless I'm sick. So, I'd be tipping off to bed around eleven o'clock. Now sometimes it's later if I'm watching something or reading something or d'ya know.".* Even participant 16 who reported a very consistent schedule seven days a week and going to bed around the same time stated that occasionally if he started watching something interesting on the TV he might sleep slightly later *"sometimes I might go a bit later, depends if there's something on tele interesting"* suggesting that TV habits could be something preventing people from keeping consistent sleeping patterns.

Subtheme 2: Maintaining a Sense of Normality

Some participants maintained a fairly consistent schedule during the week but stayed up later and got up later at the weekend in an effort to maintain some distinguishing factors. Many of these participants displayed SJL in their MCTQ analysis (Table 6.1). Participant 1 described wanting to keep the weekend different from the weekdays to make sure that every day did not feel the same *"I do want to keep the weekend different, am because every day just becomes the same."*. Things like treating yourself to a late film, and spending time on youtube seemed to guide these distinguishing factors. Participant 1 described a fairly consistent schedule of sleeping at midnight and waking at 8 during the week however consciously delayed at the weekend.

> *I go to bed later on a Friday night, am, I'm watching YouTube and stuff. And knowing that, I still want to get my 8 hours then I don't wake up till about 9:00.*

Amm it's not something I have to sort of wake up at 8 and say, oh I'm staying till nine, I don't wake up till about 9:00 on Saturday anyway. Yeah, and certainly Sunday. (Participant 1)

Participant 2 described a similar situation; he consistently slept and woke around the same time during the week due to household factors and medication but delayed at the weekend to socialise with his family. When asked about the factors that influence his sleep timing he described staying up with his wife and daughter and his perception that this was normal for many families.

Maybe a weekend now, Saturday night we might be a bit later up because we might as a family, we might be sitting around and watch a movie or watch something maybe we missed during the week or had recorded during the week. Ahh my wife takes a glass of wine or whatever maybe on a Saturday night so I would have a diet drink or whatever, my daughter might have a glass of wine or whatever. So, and we might be up until 11 or maybe half 11 at the weekend, you know what I mean. But that's the only late night because Sunday night again, the wife's getting up for work in the morning again. So it wouldn't be a late night either. So Saturday night would tend to be a late night I suppose the same as a lot of other families.

This later sleep onset time led to a later wake time the next day guiding the fluctuation in sleep timing. He allowed himself to sleep a little later on a Sunday morning but because of medication could not vary too much from during the week.

Well again its around medication really. Because ahh one of the tablets I have to take roughly about a half an hour to an hour before I take any food. So that would influence me, taking that tablet first thing. So at weekends, well Saturday, that would be no later than maybe eight o'clock I would take that tablet, so I could have my breakfast at 9. Sunday, maybe, a wee bit later I might take it maybe half 8 and then having me breakfast at half 9, but no later than that.

Participant 10 also described a very regimented sleep schedule during the week but when asked about weekend sleep onset they reported a later time and the reason he gave was maintaining that normality.

Ahh about half 10 or 11 o'clock, aaahhh I'd go to bed depending if there's anything decent on like a movie, that's it, d'ya know. So I would go to bed a little bit later at the weekends so about half 10/11."

…

for me it was just a sense of normality, being a normal person that like y'know stay up watching like a bit a tele y'know, where cause I don't drink anymore since I was diagnosed with diabetes so just a sense of normality more than anything.

This sense of normality where weekday sleep is fairly regular, but sleep might be delayed at the weekend was also observed in participants who live alone.

Well I'm often later going to bed on a Friday night, I'd ah watch a late film, d'ya know. Could be one o'clock, could be two o'clock. And kinda Saturday and Sunday then I'd be back to my week time schedule, d'ya know around eleven. (Participant 9).

Some participants did not move their wake time much at the weekend but did allow themselves more rest.

Well, amm I would wake up Rachael but I would often go back to bed after going to the bathroom, on a Saturday and Sunday. D'ya know? I wouldn't be up at say 6 o'clock or seven o'clock I'd go back to bed. I'd be up around 10 now on a Saturday or Sunday. Very rarely would I sleep like, I'd be listening to the radio or something d'ya know. (Participant 9).

Participant 9 also reported feeling a lot more rested as a result at the weekend.

I suppose cause d'ya know it's like what would you say am, it's like indoctrination hahaha d'ya know. You rest a bit more or whatever or you think you are anyhow at the weekend d'ya know.

Participant 13 who had a consistent sleep schedule throughout the week also reported resting for a little longer on a Sunday morning *"Ahh no reasons I'm afraid, I just take it easy at the weekend."* Participant 15 described a very routine sleep and wake from Monday to Sunday but did also report staying in bed for longer at the weekend.

The only thing that we might do because we got the paper delivered Saturday and Sunday, we might stay in bed a bit later we mightened get up til 9.

…

But we wouldn't be asleep til 9, you know what I mean, we we would wake probably the same time but ah we might sort of stay in bed a bit longer, read the paper, but we would not be sleeping later.

Weekend days generally but Sunday in particular was viewed more so as a day of rest where individuals would not carry out the same daily tasks and as a result shifts in sleeping patterns and resting may occur.

Subtheme 3: Derived Zeitgebers

Weekly and daily sleeping patterns were also influenced by family or other household members schedules. Some participants did not have the opportunity to sleep until their natural wake time on weekdays due to noise in the house in the mornings.

My wife and daughter would be getting up, my wife would be leaving here at half 7. My daughters up then at that stage and she's getting ready to leave for quarter past 8 so you might be snoozing but you're not sleeping-sleeping because y'know what I mean, you hear the- or they might have the radio on, boiling the kettle or you hear knives and forks, cutlery or delph or cups or whatever y'know. (Participant 2).

This individuals sleep onset is also influenced by the other household members and he describes going to bed early because his wife goes to bed early.

We go to bed because my wife's up so early, we do go to bed ahh a fairly early. Say she would be in bed by half 9 and I would probably be in bed by half 9 but I would tend to watch a wee bit of TV when she's sleeping, maybe a Prime Time or whatever. So I might watch that for an hour until half 10 and then I would usually switch it off and go to sleep myself after that.

Participant 7 also described how movement in the house during the week can also cause her to wake *"I'd usually be awake around 6 because amm my husband and son would be getting up and he has to get dropped to work. So once there's movement in*

the house, I'll be awake you know." She also described the ability to sleep for longer at the weekend without these movements.

> *Yeah, if no one is stirring in the house now I might sleep- I might wake up at 8/ half 8. Ahh probably get up then around nineish that type of thing on a Saturday and Sunday if there's nobody moving in the house. If there wasn't activity in the house you know I would sleep on a little longer yeah yeah.*

Other responsibilities beyond just noise in the house were observed to influence and curtail wake time during the week. Participant 8 had to bring her daughter to school, so she needed to use an alarm clock Monday-Friday to end her sleep. She reported sleeping and resting for longer at the weekend.

> *Well, in the week if I'm taking my daughter to school, we'll wake up about 7, amm at the weekend, see ah (*sigh*) I'm kind of strange I wake up early in the morning. I can wake up about half five to go to toilet and if I go back to sleep, if it's the weekend I'm not gonna wake up again about eight. And then I'm gonna have a cup of tea and then fall asleep again. So I'm kind of I sleep very staggered really. I don't seem to be able to- you know, I can't just go to the toilet in the morning and then immediately got back to sleep, I just can't seem to do that. Amm I've always been a bit like that really.*

Participant 14 has a son who works shifts and this led to her varying her sleep onset as she would always wait for him to return home before going to bed. When asked about sleeping patterns from Monday to Friday she responded:

> *Well my son finishes work at half 12 at night and when he comes home, shortly after that, I go to bed.*
>
> …
>
> *I like to see him before I go to bed.*

She slept earlier at the weekend if he was working an earlier shift or off completely. *"It could be 12 o'clock on a Friday night because* [redacted] *comes home earlier on Friday night. Saturday night it could be half 11."* This resulted in this participant displaying negative SJL across the week (see Table 6.1). The schedule of these household members was being put on these participants either through necessity with providing transportation to school and work or through choice by choosing to stay up

until their shift was over. Participant 3 as previously described likes to be very organised with her sleeping pattern also described how if people are visiting or family members are over this can occasionally disrupt her sleeping pattern *"If you're on your own, it's easier to make those make those decisions for yourself."*

Participant 11 described a different but related event. Participant 11 and his wife slept freely during the week but used an alarm clock every Sunday morning for mass. This also influenced their onset the night before *"uhm if I'm going to be up for 8:30 mass, if I'm getting up at 7 I try to get to bed around 12 o'clock and have 7 hours"*.

Theme 3: Disrupted Night-Time Sleep

"Well I could be getting up during the night, and I mightn't sleep for a while. My sleep wouldn't be great." (Participant 14).

While some participants reported being a good sleeper many participants described a very disrupted night-time sleep where they might have trouble initiating sleep and experienced several wakening's after sleep onset.

> *I'm a poor sleeper aa really. If I get to bed, if I don't get to sleep fairly quickly, sleep does pass me by, and I could be hours before I sleep. But ah I don't know what it is but if I go in, lie down and am gone in a few minutes that's fine. If I don't, I don't know what it's like. But I could have to get up again because I wouldn't settle, you know.* (Participant 7).

These disruptions during the night may have influenced their final waking time and three subthemes were generated to explain this which were: "rumination", "waking to use the bathroom" and "other health issues/age" (see Figure 6.3). These may have had potential influences on waking time as participants described a situation where it was hard to get back to sleep especially if waking was close to their normal rise time.

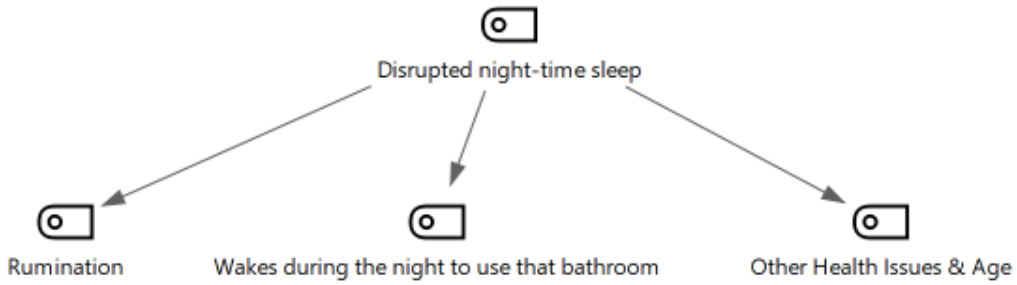
> *Usually go back to sleep again pretty quickly, but if it's very close to morning say 5 or half 5 sometimes, I do find that hard to get back asleep again.*
> (Participant 15)

One participant also spoke about spending time up during the night and getting up later as a result.

Uhm I'd say half three in the morning and it was up then for an hour and a bit, made tea and went back to bed again. And ah half 10 about I got up then. (Participant 14)

Figure 6.3

Thematic map of our third overarching theme disrupted night-time sleep and its three subthemes which were rumination, waking during the night to use the bathroom and other health issues and increasing age.



Subtheme 1: Rumination

When participants were asked about how long it takes them to sleep or how easily they sleep it became clear that some participants experience variations is sleep onset due to rumination and stress *"Ehh it can take am, a while like you know depends again like y'know how you feel like but sometimes you might be a while, like you might be thinking and ah that type of thing"* (Participant 11). Participant 8 also described her problems with sleep due to having things on her mind *"Uhm, and I mean, I'm- I am quite anxious person as well, so I think having things on my mind all the time probably doesn't help, so I can't switch off I suppose."* Stress did seem to impact the ability to fall asleep and maintain sleep which would naturally lead to more varied day to day sleep onset.

Amm yeah, I mean there are, there are some stresses, family wise, am which I have. I've got an older stepson and he's going through some difficulties at the moment, so you know that prays on your mind a bit. Am yeah, so things like

that, yeah. Am, but am yeah, nothing, yeah, so I mean, so those sort of those stresses do- would affect sleep definitely. (Participant 4).

Participant 3 acknowledged how negative news could influence her sleep and avoided this before bed which helped her maintain consistency.

I think you could be disturbed by the newspaper especially with what's going on around this and I think I have to make sure I'm not reading negative-negative news before I go to bed. I think that could impact you a lot.

Many of the other participants reflected on times in the past where they would have been stressed and their sleep timing would have been influenced as a result. One participant described a time in the past where she spoke to her GP about her sleep due to the family stresses she was experiencing *"at one time, that time that I was anxious I spoke to my GP about a sleeping tablet"*. (Participant 15)

Subtheme 2: Waking During the Night to Use the Bathroom

Many participants described waking during the night to use the bathroom. Nocturia is a very common side effect of diabetes and it seemed to be prevalent in this sample.

No matter what and as I say most of my friends who are my age group all say they get up at night, so I think it's kind of that interrupted sleep goes with getting older. So, I don't know if it is related to the diabetes or is it just related to the fact that I get up and em ah. So, you know, so I do have broken sleep every night, but I mean I don't know whether this diabetes is causing it, I've never actually talked to the doctor about that. I just get up to go to the toilet so so I don't ever sleep right through from, say, midnight to six or seven without waking-, without getting up at least once. (Participant 15).

Participant 16 described a similar pattern that he could control to some extent by reducing fluid intake in the evening.

And if I was lucky enough that I don't have too many drinks of tea, or water, or milk or something, ehh I won't get up as often, but I still get up.

While this impacted some people all of the time, some participants did not report this problem at all, while some experienced it occasionally *"Well maybe an odd time I might have to go to the toilet during the night, that's all. That's the only reason"* (Participant 13). When participant 9 was asked about her wake time bathroom use was noted to possibly impact this *"Now sometimes I have to go to the bathroom as well like d'ya know so. The bathroom has an influence I suppose."*. These awakenings might then influence final wake time and can influence our daily sleep and wake schedule.

Subtheme 3: Other Health Issues & Age

Other health issues and conditions can also disrupt sleep. Participant 15 described how her arthritis may further disrupt her sleep beyond the bathroom use.

> *Ahhh well, the-the only thing that would influence me would be that sometimes if I'm having a bad run with the arthritis I might wake up during the night with my knee, like my knees might be paining me and I take two paracetamol and go back asleep again. But sometimes when I say I'm up twice a night yeah, I wouldn't include when I might ahh- when I say about twice a night, it's usually to go to the loo, but if I was going through, you know, a flare up with the arthritis I might wake a third time and that would be just my knees would be paining me and I'd take two paracetamol and go back, asleep again, but ehh that wouldn't happen all the time.*

Participant 15 also made reference to the increased awakenings happening more as she has gotten older *"as I say most of my friends who are my age group all say they get up at night, so I think it's kind of that interrupted sleep goes with getting older."* One participant was experiencing menopause, and this disrupted her sleep.

> *Yeah, I would often wake up every hour. I'm menopausal am hah you know that kinda thing ha I'd be very hot you know that sort of thing. I don't sleep right through the night ever; I wake a good bit. But I guess that's kinda you know the way it you know the way. It's not that once I go to sleep, I'm asleep for the whole night, I'm not, you know.* (Participant 7).

Participant 6 described the nerve problems due to diabetes and if he did not have the correct medication, he would not sleep at all *"My left leg is affected by the diabetes, I wouldn't sleep one wink if I didn't take the tablets."*

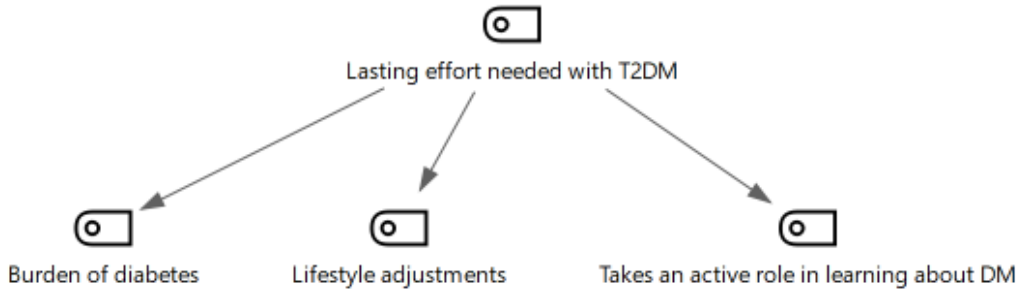
Theme 4: Lasting Effort Needed with T2D Diagnosis

"But it's the one thing you can't do in diabetes is take a break from anything. You have this every day, all day and there's no break from it" (Participant 7).

Many participants made reference to the constant awareness around their diagnosis, noting how serious the disease was and that *"it's a lifestyle really"* (Participant 7). Three subthemes were identified which were "the burden of diagnosis", "lifestyle and eating adjustments" and "takes an active role in learning about diabetes" (Figure 6.4).

Figure 6.4

Thematic map of our fourth main theme lasting effort needed with diagnosis of T2D and its three subthemes highlighting how the diagnosis was for life and managing this could be difficult. The subthemes were the burden of the diagnosis, the lifestyle changes people made and were still making and the active role that some participants had in learning about the disease.



Subtheme 1: The Burden of Diagnosis

One participant discusses how living with diabetes has its ups and downs but is manageable with a little bit of daily effort.

> *D'ya know there's variations there's up and down, you're going to experience that as you go along like you know, know as you try to live with your type 2. Like d'ya know it's not the end of the world if you do the things alright, you'll be ok, d'ya know.* (Participant 11).

Participant 7 also spoke about these variations in coping and how this is related with the control she may have.

> *It doesn't bother me much so much when it's OK but when things go off kilter I hate every bit about it. You don't be good then either when you're in that sort of a mood. D'ya know, you just kinda think I'm fed up of this you know because it's not something you can walk away from. It, it's there all of the time. There's no break from it or anything, you just have to do with it every day you know, so. It's a lifestyle really, but ah anyway as I said so far so good the last couple of years. It's been quite good and they're quite happy, ya know.*

Poor control may then put a greater burden on the individual to get things under control again. The potential burden was very clear from other people's accounts. Participant 6 spoke about how *"serious"* the disease was and how imperative regular check-ups were "*so you have to watch it, you have to go to the doctor and take bloods every so often".*

Another participant spoke about how difficult managing the disease is and the struggles he faced *"It's a horrible, horrible, horrible disease to tell you the truth and it's not something you can control easy, you know what I mean.".* He also spoke about the cravings for sweet food he experienced and how difficult it was to control his diet, stating that *"if you were badly badly off you'd do anything to get something sweet."* Certain people with diabetes may need more tailored support to deal with this burden and greater medical support may be beneficial.

> *I'll tell you what, a lot of it is down to myself and the doctors are leaving it to me, to do myself. They're not, they'll tell you that this is high, that's high, they're not telling you how to go about doing things. You need somebody that's able to tell you, you know, the best way of doing things, to look after things the right way, you know what I mean.* (Participant 16)

Participant 16 went on to say: *"if you've somebody who's trying to help you and you know they're trying to help you, you'll try yourself."* The burden that these thoughts may have on participants with diabetes could very clearly negatively impact various aspects of daily functioning.

Subtheme 2: Lifestyle Adjustments

Many participants spoke about the lifestyle changes they had made or were in the process of making in order to optimise their health. Participant 1 took the opportunity after retiring from work to increase his activity levels.

> *Well, amm exercise is another fairly important thing, but I was I have like I was always attempting to do 10,000 steps a day even when I was in work. It wasn't always possible amm you might get to about 6 amm, 6 or 7 and occasionally you would get to 10. And you'd kind of be like ooh I made it. Am now, 20, 30 wouldn't be out of the question and then I could cycle as well.*

Participant 1 described the diabetes diagnosis as a *"shock to the system"* that caused him to reflect on his own mortality. Participant 2 spoke about his *"sweet tooth",* tendency to snack and the weight he was carrying before the diagnosis but also spoke about how that had since changed. Participant 3 described how she was still managing to keep her diabetes under control with a healthy diet and exercise.

> *I can't remember what it was and she said that's usually when you need medication and I said, well, I'll try to improve my diet and my exercise and she let me do that so. I did le-, I lost a stone and it came down a bit.*

Similar to participant 3, participant 8 described some big changes in activity levels since the diagnosis in order to make sure that the diabetes does not disimprove. *"I'm kind of strange cause at the moment I'm doing walking as well and I've also joined up with a* [redacted] *the Leisure club."*

Participant 16 spoke about his weight loss *"I'm not that heavy you see I'm only 13 stone now, I used to be 18 stone years years ago, so I lost the weight."* But he did make reference to further changes that he needs to make especially regarding food.

> *But my diet isn't great you see, you know at times. Sometimes I end up getting some kind of takeaway, you know. But I've been changing my ways lately so whether it I'll help me or not I don't know.*

Participants were conscious of what types of food they consumed and how that might influence their diabetes management and health overall. "*Well, look it. I I am conscious of it, well now I say conscious, I'd be, it would be always sort of there like*

when I go to sit down to eat or anything like that." (Participant 12). Participants also spoke about the importance of keeping their blood sugars under control and the ways they manage their diet daily to achieve this. For example, participant 17 spoke about how if he was travelling somewhere he would always have a lunch or meal with him. Participants also had ideas about how certain types of food were good or bad for diabetes.

> *Diabetes is also about portion control and so much on your plate and there's stuff the size of your fist and all that. I eat more or less what I want amm it's the right kind of stuff ah, but quantity wise I'm not too fussed.* (Participant 1).

These food choices might vary slightly but participants generally aimed to maintain a healthy diet.

> *Well, I mean, I would eat a sort of a healthy enough diet anyway. Obviously, you know I avoid too much sugar, and fat etc, I actually have a son who has diabetes, so I mean, we always ah kept to, kept to a reasonably good diet. I mean I do vary my diet. I would actually get very bored if I was to eat the same thing, you know the way some people eat the same thing a lot. I know I said I eat potatoes and vegetables and whatever, but I'd have to eat rice y'know then another day.* (Participant 5).

It was also clear that participants made slight alterations to how they prepared their meals since the diagnosis.

> *ahh there's not so much limitations but am diabetics should avoid certain things and should am have am more of other things. So, I've a higher fibre than I would have. I don't eat am what would be called the crap, am, I haven't had, I haven't had like a takeaway since I was diagnosed, don't actually miss it an awful lot. Am Sunday would be still amm, I'd have a fry in the morning, or it will be grilled. I'd have a bowl of porridge after I come back from my walk and have a proper Sunday dinner then at around half 5/6.* (Participant 1)

Participant 10 also spoke about how he has switched from frying some food to grilling them.

I'm doing a lot of the grilled stuff now instead of frying it, y'know like if I was having bacon or rashers or something, I would aaah, they'd be in the grill, they would be different to y'know the frying pan.

Various alterations in diet were noted by participants from reducing potatoes *"ah I try and keep to two medium potatoes because there's too much starch in potatoes, so I try, I was eating a lot of potatoes before but a I've cut back on that now to two potatoes."* (Participant 15), to moving toward a more vegetarian diet *"amm increasingly I have been trying to make vegetarian meals and get away from meat and anything like that."* (Participant 3), to cutting out some types of food *"So the likes of pizza and stuff like that aah I stopped eating."* (Participant 10). Participant 6 does his best to not touch anything with too much sugar in it. These alterations were described as difficult by some participants. For example, participant 6 noted how getting out of the habit of snacking and avoiding too much sugar was difficult in the beginning.

T'was first- it was first alright when you were used to bits and pieces and were snacking and all this caper. Its aa very hard to get out of it but you have to, if you don't t'would be hurting, d'ya know what I mean hah.

Participants also noted following the advice of their doctors around their food choices and one participant prepares separate meals for himself and his children to allow for this.

Amm like the kids would have different now but I like I am trying to eat the diet that the dietician gave me.

…

As I said the food I'd eat now the kids wouldn't even look at (Participant 10)

Breakfast consumption seemed to be an important aspect of maintaining a healthy diet for this group and only two participants reported ever skipping breakfast. Participant 14 reported *"sometimes"* skipping the meal while participant 16 also sometimes went without breakfast which actually led to overconsumption later in the day *"Sometimes I go without breakfast, ehm just with the rushing and then you'd eat too much you know what I mean".* The other participants were very enthusiastic about their morning meal.

we would eat breakfast, we're big breakfast eaters both of us, so we have quite a substantial breakfast at about nine or half nine. So like typically we'd have maybe fruit and yogurt, maybe an egg or some kind and toast, we kinda have a big breakfast. (Participant 15).

Yes, my breakfast never changes, never ever changes. I get up in the morning. I have a bowl of porridge and a cup of tea and I have a slice of brown bread. That's every morning, seven days a week, 365 days a year. That's final, I never miss breakfast. (Participant 12)

Some participants were also conscious of not eating too late at night and identified how late-night eating could prevent them from achieving a healthier weight.

five o'clock is the latest for me. I don't eat any later as I said a while ago that I might just have a rich tea biscuit and a glass of water maybe or maybe if I was really hungry, I might have soup, cream crackers, and a bit of cheese in between the two of them. That's all. (Participant 13).

Well, I I'm aware of the fact that eating heavy food late at night is not good, so we we do tend to avoid that. Uhm and yeah, we don't- we don't really, it's hardly ever that we'd have a late meal, it's not something that me or my daughter like doing. So, uhm and I know that it's not good for the weight as well it contributes to the weight staying on because you're not working it off and things like that. (Participant 8)

Some participants reported eating snacks closer to bed and even though they would be aware of the negative impact this would have on their health *"I'll tell you, probably too late before I go to bed, that'll be the problem. Probably too late before bed, you see"* (Participant 16). This again highlights that some participants were more conscious of meal timing than others.

Subtheme 3: Taking an Active Role in Learning About T2DM

Participants showed an interest in learning about the disease beyond what the doctors and nurses were telling them *"I didn't know nothing about diabetes until I got it, but I tell you I've a lot learned since I got it."* (Participant 6). Participant 6 spoke

about attending HSE meetings to learn about meals and the influence certain foods can have:

> *They have a-a-a-a a thing called CODE meetings and we do we'll say we do aah two hours am two hours or a day different days of the week that a, that a shows us-tells us how to aa buy the food and what to look for. We'll say the carbohydrates and the sugar and all that caper. To make sure that you didn't get stuck with aah something with a rake of sugar in it, so it helps. There isn't much stuff without sugar in it. Biscuits or anything like that, you can't go near them at all, full of sugar. Sweet cakes all of that sort of stuff, you can't go near that. D'ya know.* (Participant 6)

Some participants also seemed to be keeping up with research online and any advancements that might be occurring and also thought that the doctors maybe did not incorporate new findings into their treatment as much as they could.

> *It takes the health board a long time for their nutritionists or their dieticians to change their what you call, thinking, cause they're trained a certain way to believe a certain thing and they're too rigid in their beliefs. So I think there's more hope out there for people. And I felt that when I reduced carbohydrates it had a big impact on my body and my sleeping, so I think I might try that again.* (Participant 3).

Participant 1 noted that he has learned more online beyond what the diabetes team has told him *"They don't really mention sleep, it's only looking at stuff on the internet where you see sleep is also very important."* Participant 3 also recounted recently reading a book on sleep that made her *"realise the importance of it".*

6.4 Discussion

In this study, we used semi-structured interviews to investigate sleep timing and daily routines among individuals with a diagnosis of T2D and without a regular work schedule. Some participants described having consistent sleeping patterns. In this instance the daily routine of waking and sleeping was partially just a habit. Retirement and age, unavoidable morning curtailments, and ownership over their environment before bed also led to more consistent schedules. Other participants described the opposite where they experienced fluctuating sleeping patterns which were influenced by factors including the quality of TV programs, wanting to maintain a sense of normality so that every day was not the same, and derived zeitgebers which were schedules imposed on our participants due to working household members or other responsibilities such as driving children to work or school. Night-time disruptions which included rumination and was characterised by not being able to switch off before sleep, waking during the night to use the bathroom, or due to other health issues and age were also prevalent in this sample. The final theme described the lasting effort that participants required to keep control of the disease. Diagnosis imposes a significant burden on some participants, requires lifestyle changes and also encouraged some participants to take an active role in learning about the disease. These findings provide some rich information on daily routines, sleep timing and what can help people keep more consistent schedules. More regular bed and wake times can have beneficial effects as it can lead to optimal synchrony between the night-time sleep episode, the physiological drive for sleep and the internal circadian rhythm (Chaput et al., 2020; Irish et al., 2015). Further, regular bedtimes and wake times among older participants (65+) has been associated with better sleep quality (Monk et al., 2011).

Of the consistent sleepers some participants developed a routine, and it became a habit. Habit formation has been suggested as a potential mechanism to get individuals to adopt some healthy lifestyle decisions (Gardner et al., 2012). Therefore, it might be worthwhile to develop some recommendations to encourage this habit formation in the wider sample with T2D. This habit was in part influenced by an individual preference to have organization around their day even if they did not have specific tasks to attend to at certain times. Retirement and age acted to enhance this consistency by reducing daily differences and leading to participants following a regular routine. Participants essentially described fewer distinguishing factors day to

day and a routine sleeping pattern as a result. This was expected as previous research has shown that SJL and sleep timing differences between the week and the weekend decreases with age and retirement, largely due to the end of structured employment (Garefelt et al., 2021).

Only one participant reported needing to wake in order to check blood sugars. This did lead to her displaying a more consistent schedule. Two other participant were conscious of taking medication at a certain time before food. Medication use had been shown to previously guide food timing (Lee, Willing, et al., 2016) but less was known about how it drives sleep and wake schedules. In general, for the majority of this sample medication tended to be taken an hour before breakfast or with breakfast but did not dictate 'when' this meal or wake time occurred. This suggests that disease monitoring and medication is not a big factor in determining sleep/wake timing among participants with T2D.

Participants with consistent daily patterns also often reported methods of enhancing their environment before bed for sleep and in a sense improve sleep hygiene. Sleep hygiene broadly includes following behavioural and environmental suggestions to improve sleep (Irish et al., 2015). These participants turned the television off at a certain time and did not stay up for no reason. They also reported not having any screen stimulation in the bedroom and reducing time on the computer or tablet in the hours before bed. This all helped enforce a regular sleeping schedule. Recent research has been highlighting the role that sleep hygiene may play in promoting health in the general population (Irish et al., 2015). Research has also suggested that holistic diabetes management that goes beyond oral medication and insulin is required for people with T2D (De Sousa & Kalra, 2017). Sleep hygiene programs have been suggested as an important aspect of this holistic approach for people with lifestyle disorders like T2D (De Sousa & Kalra, 2017). These sleep hygiene suggestions included keeping a consistent wake time, only have dim-light in the bedroom and managing stress. Sleep hygiene may therefore be beneficial for individuals with T2D to promote wellness which is advantageous as many of the suggestions are easy to follow and unlikely to place substantial burden on individuals (Irish et al., 2015). Managing stress as part of a sleep hygiene program may also help reduce the rumination that some participants experienced before bed.

Furthermore, television viewing, computer use and screen stimulation before bed are important to avoid as research has shown how light in the evening or night, especially blue wavelength light often emitted from these devices can suppress melatonin and delay sleep times (Brainard et al., 2015; Gringras et al., 2015). The National Sleep Foundation recommends all devices be turned off for an hour before bed. The viewing of the television as observed in some of our participants has also been suggested to influence sleep timing in the past (Garefelt et al., 2021). In our study 'good' television programs were reported to drive sleeping patterns. However, this television viewing could be supressing melatonin and increasing alertness which can influence sleep onset. Simple behavioural or educational interventions which may promote not staying up for no reason could be developed here. The availability of these TV programs on demand could allow participants to still watch these programs but to watch them at a more optimal time during their circadian rhythm. This is actually a behaviour we observed in some of our consistent sleepers. Interventions which involve more organisation around the day, and better ownership of their environments before bed may be advantageous.

This analysis also provided important information that some individuals value getting to treat themselves and not necessarily conform to 7 days of consistent sleep and wake. This was also noted as an important means of socialising with family members. Whether the physiological benefits of maintaining consistency outweigh the psychological benefits in these people needs to be considered. Furthermore, it need to be established whether or not individuals can keep a sense of normality and distinguish the weekend from the week without varying sleeping patterns.

Individuals who are not working do not have direct rise-time constraints stemming from work or school (Monk et al., 2011). However, the schedule of household members might have an influence. The derived zeitgebers and commitments the participants have cannot be easily targeted. These *"derived social zeitgebers"* whereby household schedules influence sleep timing has also been described by previous research (Garefelt et al., 2021). More specifically, when individuals retire but their partners are still in full-time employment smaller reduction in sleep timing differences are observed in comparison to those who had a retired partner (Garefelt et al., 2021). It seems that other working members of the household may impose their schedules on the nonworking participants. Educational interventions

to family members to reduce noise in house in the morning may be beneficial here so that non-working household members can sleep until their natural wake.

Many participants reported rarely sleeping through the night and described being 'up and down' a lot. Research suggests that around 31% of adults from Western Europe experience disrupted sleep (Irish et al., 2015). Furthermore, night-time disruptions are more prevalent with age and since over half of our sample was retired, this was not unexpected (Jonasdottir et al., 2021; Monk et al., 2011). Older participants in this sample may experience these night-time disruptions due to reduced homeostatic sleep pressure (Jonasdottir et al., 2021; Pace-Schott & Spencer, 2011). The homeostatic drive for sleep is very important in controlling our sleep-wake schedules all throughout the lifespan.

Another disrupting factor was bathroom use and participants seemed to wake frequently at night for this reason. These participants may be experiencing nocturia which involves waking at least once during the night to void, and this is a common and bothersome urologic symptom (Tikkinen et al., 2006; van Kerrebroeck et al., 2002). While nocturia is increased with age it can also be influenced by other factors including obesity and diabetes (Aoki & Yokoyama, 2012; Tikkinen et al., 2006). Increased BMI among individuals with T2D has also been associated with increased occurrences of nocturia (Bulpitt et al., 1998). Many of our participants accepted nocturia as a common side effect of ageing. This finding was also reported in a previous review by Kim et al. (2016). Further, nocturia is associated with frequent insufficient sleep and is a cause for concern. Research is emerging to suggest that nocturia may actually be indicative of circadian rhythm dysfunction whereby disrupted circadian rhythms cause voids or vice versa (Kim et al., 2016). Mammals typically urinate more during the day than at night and this relies in part on the function of circadian oscillators in the kidneys. Other health issues and age also causes night-time disruptions. Some participants were occasionally experiencing arthritis, nerve pain and menopause which led to more awakenings during the night.

Another factor leading to disrupted sleep was rumination before sleep and not being able to 'switch off'. Some participants described having things on their minds or feeling anxious and having trouble sleeping as a result. In chapter 5 no association between perceived stress and chronotype or SJL was observed when controlling for

confounding variables. However, chapter 5 investigated the association between average sleep timing across the week and weekend, it did not have the scope to investigate day-to-day fluctuations. This stress and worry may cause cognitive and physiological arousal which is a problem for sleep initiation and continuation (Irish et al., 2015; Kalmbach et al., 2020). Stress management programs may be beneficial for this group to help maintain a more consistent schedule. This is an important theme because if sleep is disrupted it might lead to insufficient sleep as well as alterations in sleep onset and wake time.

The lasting effort required for managing diabetes is also important here for two reasons. Firstly, the diagnosis does add significant daily burden to people's lives and influences their daily routines. T2D is a chronic condition and as a result people living with T2D can experience daily challenges and the care required to manage symptoms and reduce risks of complications is unremitting (Corbin & Strauss, 1988; Ribu et al., 2019). This might influence their sleep timing and quality. Some participants may need additional medical support from their GPs or psychological support. Secondly, it has a potentially positive influence on the feasibility of interventions because it shows that people are willing to make lifestyle changes and learn about the disease. However, it also demonstrates that these individuals are already under a significant burden with the disease. This in addition to the rumination and other night-time disruption the group experiences highlights that interventions should not add unnecessary stress to this burden and therefore need to be as easy to follow as possible.

6.4.1 Strengths and Limitations

This study has a number of strengths. Firstly, seventeen semi-structured interviews were conducted, and these interviews provided rich information on these individuals' daily schedules. Reflexive thematic analysis was utilised which allowed for a data-driven approach to analysis. This allowed us to give the participants a voice and really focus on what they said to guide theme generation. All interviews were conducted online or over the phone due to the restrictions of the COVID-19 pandemic. This prevented bodily cues from being observed. However, there was a strength to this for two reasons. Firstly, individuals from Ireland and the UK could be recruited allowing a wider sampling pool. Secondly, previous research has identified the benefits of phone interviews in comparison to face-to-face interviews for sharing

personal details (Drabble et al., 2016). The participants may have actually been more comfortable talking about their daily patterns over the phone or the computer than in person. Furthermore, a recent study investigating the enablers and barriers with self-management of both type 1 and type 2 diabetes obtained rich data from phone interviews (Adu et al., 2019) which suggests it may be an appropriate method for this particular population and helps reach people living in remote locations.

6.4.2 Conclusions

In summary this study demonstrated that regular sleeping patterns are feasible as many individuals with T2D were already displaying these. However, many participants displayed fluctuating sleeping patterns due to TV viewing, not wanting every day to be the same and derived zeitgebers. Some of these factors are easier to overcome than others. Behaviours of those with more regular schedules like habit formation, and ownership over the environment before bed may be applied to overcome letting quality TV determine sleep timing. This would allow for stronger synchrony to the underlying circadian rhythm. However, overcoming the derived social zeitgebers of family members is harder as these individuals still have the structured daily schedules. One interesting point was wanting to keep some distinguishing factors between the week and weekend. This sense of normality may be very important to these participants psychological wellbeing and recommendations for a consistent schedule cannot ignore this. Whether this normality can be achieved through activities that do not disrupt sleeping patterns should be investigated. Night-time disruptions were common and must be understood as having the potential to influence sleep timing as well as sleep quality. This qualitative analysis also provided us with valuable information on peoples experience with T2D and the lasting effort that is needed following a diagnosis. This lasting effort has the potential to influence daily routines and to place significant burden on individuals. All interventions and treatments need to take this under consideration. However, there is also a positive aspect to this as it shows that this group are willing to make lifestyle changes and interested in learning more about the disease and its management.

Chapter 7:
General Discussion

7.1 Summary of Findings Presented in this Thesis

The overall aim of this thesis was to examine how sleep timing and circadian rhythm disturbances in people with T2D contribute to their disease severity and management. Through this, we hoped to improve T2D disease management and decrease the occurrence of debilitating diabetes complications. Small improvements in HbA1c can reduce the risk of complications and the burden associated with T2D (Stratton et al., 2000). The global prevalence of diabetes is expected to rise from 9.3% in 2019 to 10.2% in 2030 (Saeedi et al., 2019). As such, gaining a deeper understanding of what factors influence glycemic control and disease management is a crucial topic of research. This chapter begins with an overview of the findings from the five empirical chapters. Next, the implications are discussed. Following on from this, there is a discussion of the strengths and limitations and the final concluding remarks.

We first investigated the previously described association between later chronotype, and poorer glycemic control among a sample of participants with T2D (Reutrakul et al., 2013). In this current work we used a similar methodological approach by utilising MSFsc as a measure of chronotype and the PSQI to measure sleep quality. However, since chronotype and personality have been associated in the past, we considered the role that personality may have in explaining this association. Previous research suggests that highly conscientious people may have better control of their health (Bogg & Roberts, 2013; Skinner et al., 2014) and since morningness has been associated with conscientiousness, we wanted to assess if this could explain why evening chronotypes tended to have poorer glycemic control. Furthermore, while SJL has not been explicitly associated with some personality factors, it is closely linked to chronotype and was considered as a potentially important variable. Interestingly, we identified that SJL, and not chronotype was a significant predictor of poorer glycemic control in our sample. Additionally, we identified a novel interaction between chronotype, SJL and HbA1c whereby in individuals with the greatest SJL, later chronotype was associated with higher HbA1c. Chronotype and HbA1c were not associated in any of the other SJL groups. Personality was not a significant predictor of HbA1c in the final model. This led to the conclusion that circadian misalignment might act directly on glycemic control and have an adverse influence on diabetes disease management in an Irish sample with T2D.

Two interesting points arose from this study; firstly, that while personality was not a moderating variable, that the association between greater SJL and poorer glycemic control in younger working participants may be moderated by workplace psychosocial stress. While psychosocial stress has not been associated with poorer glycemic control in the past (Annor et al., 2015), its association with SJL was largely unknown and it warranted further investigation. A second point was that older individuals also demonstrated weekly misaligned sleep timing. This suggests that social factors beyond work schedules can influence sleep timing and daily routines and it cannot be assumed that older adults will display consistent schedules across the week (Jonasdottir et al., 2021; Chapter 2).

In chapter 3 we had an opportunity to examine additional measures of sleep timing. Chapter 3 identified that those with T2D self-reported greater SJL than controls but that this was not observed by our objective measure. This chapter also investigated day-to-day variability in sleep timing which has been suggested as another indicator of circadian misalignment (Brouwer et al., 2020). This study was exploratory in nature and the only variability measure associated with SJL here was sleep end variability. Sleep onset variability, sleep duration variability and midsleep variability were not associated with SJL. This suggests that these measures are not necessarily measuring the same underlying construct and when researching circadian misalignment, there may be scope to investigate more than one measure. No groupwise differences in sleep timing variability were observed but interestingly, less midsleep variability was associated with poorer glycemic control in those with T2D which is the opposite of our expectation. It does suggest the need for future research to fully investigate these measures of variability to ascertain if this is a true relationship or what the nature of the association is.

In order to determine if SJL and stress were associated and if stress was a worthwhile covariate in future research, chapter 4 assessed the association between SJL and perceived stress and the three domains of the job demand-control-support model. Multivariate analysis revealed no significant associations with SJL, rendering the findings from chapter 2 unlikely to be attributable to workplace stress. Furthermore, the pilot study on stress reactivity does not suggest that SJL has a large impact on reactivity to a psychological or physiological stressor.

In chapter 5 the UK Biobank enabled us to investigate sleep offset differences between week and weekend days. This is similar to SJL as it examines the difference between week and weekend days, but it differs in two ways. Firstly, we consider weekend days as free days and weekdays as workdays as no information on work schedule was available, and secondly, we are investigating sleep offset differences rather than midsleep differences. We noted some interesting differences in actual and absolute weekday to weekend day sleep offset differential based on gender, deprivation index, and age for example. Males, those with the most deprivation, and those who were younger, displayed more absolute and actual week to weekend day sleep offset differences. While those with the greatest delays in sleep offset at the weekend were on average younger, positive, and negative weekday to weekend day sleep offset differences did not appear to have differing influences on the cardiometabolic variables in any age group. This indicates that greater weekday to weekend day sleep offset differences, irrespective of the direction, can impact health in a similar manner and adds value to using the absolute SJL variable. One thing noted from this sample was the great power, however it was limited by its phenotyping. Overall, chapters 2, 3, 4 and 5 did some work to describe sleep timing differences and different proxies for circadian misalignment.

Chapter 6 served to provide a rich description of the factors beyond work that influence sleep timing and daily routines. Using thematic analysis, four main themes, each with their associated subthemes, were generated which were consistent sleeping patterns, fluctuating sleeping patterns, night-time disruptions, and lasting effort needed with T2D. Subthemes explaining consistent sleeping patterns were habit, taking ownership over the environment before bed, reduced activities due to age and retirement and unavoidable morning curtailments that occur irrespective of the day. These included walking a dog, for example. The subthemes explaining fluctuating sleeping patterns on the other hand included: letting the quality of TV programs guide bedtime, wanting to maintain a sense of normality and differentiate between week and weekend days and also derived social zeitgebers from family members. Employed family members, for example, possessed the ability to impose their schedule on some of our participants. Some of the night-time disruptions were explained by subthemes including needing to wake during the night to use the bathroom, rumination before bed and certain additional health issues. The final theme lasting effort needed with

T2D also had three subthemes which were the burden of the diagnosis, lifestyle changes and taking an active role in learning about the disorder and these subthemes also impacted the daily routines of our participants. This was useful because it was the first qualitative study to investigate the factors influencing sleep in a cohort not in employment. This reinforced that for many people sleep is a social factor and not just driven by biology.

7.2 Implications of Findings

The findings of the present thesis make a substantive contribution to the literature on circadian misalignment and T2D and have several vital clinical implications. Growing research has implicated sleep debt and circadian misalignment, beyond typical unhealthy lifestyle factors such as unhealthy diet, sedentary lifestyle, alcohol intake and smoking, as risk factors for various NCDs including obesity, diabetes, cardiovascular disease, and metabolic syndrome (Parsons et al., 2015; Roenneberg et al., 2012; Wong et al., 2015). Beyond putting people at risk for T2D and other NCDs, these factors have also been implicated in the control of various metabolic disorders (See section 1.14; Mota et al., 2017; Mota et al., 2021). One of the major patterns revealed in this study was that SJL, independent of personality factors and chronotype, predicted poorer glycemic control among Irish patients with T2D. Research in a later chapter also identified that SJL and both perceived stress and work-related stress were distinct concepts in group of students and workers suggesting that the relationship between SJL and glycemic control may not be mediated by the stress individuals can experience. Weekly circadian misalignment may therefore have an impact on metabolic health and glycemic control in T2D independent of personality or work stress. Misaligned sleep timing promotes other activities such as eating during the wrong time in the circadian cycle. This has been shown to increase the risk of cardiometabolic disease (St-Onge et al., 2017) and cause hyperglycemia among individuals with diabetes (Beccuti et al., 2017). These associations can be explained in part by the uncoupling of central and peripheral clock rhythms (Zaki et al., 2020). This raises the possibility for simple behavioural and sleep targeted interventions to treat the condition by reducing circadian misalignment and glycemic control and therefore limiting the risk of secondary debilitating consequences. This is an attractive alternate avenue for treatment as it could help improve glycemic control without

additional pharmacological treatment. It also provides the participants with more autonomy over their disease management.

The development of these interventions are complicated by a few factors. For example, SJL has been reported to have varying effects on different markers of metabolic control depending on the population and the specific characteristics of this population. Notably, in the study we partially replicated later chronotype and not SJL predicted poorer glycemic control (Reutrakul et al., 2013). This causes us to reflect on how different cultures can display different amounts of SJL and different associations with indicators of metabolic control.

These findings also reinforce how common circadian misalignment is in modern society. This research showed that younger participants displayed more SJL and larger weekday to weekend day sleep offset differences, which mirrors previous research (Jonasdottir et al., 2021; Wittmann et al., 2006). However, it also demonstrated that older participants displayed weekday to weekend day differences in sleep timing, suggesting that circadian misalignment may influence people all throughout their lives and not just during their working years (Garefelt et al., 2021; Jonasdottir et al., 2021). Our studies consistently demonstrated this; in chapter 1 the participants average age was in the 60s and SJL was recorded. In the UK Biobank, many older participants not in employment noted week-to-weekend day sleep offset differences and a small prevalence of SJL was observed using our qualitative study in chapter 6. This all shows that sleep and sleep timing is a social factor beyond simply a biological one, and there are factors which can constrain it either by choice or obligation. We cannot simply assume that older adults who are considered healthy or who have a NCD such as T2D sleep consistently across the week.

Social zeitgebers, including social interactions, have the ability to influence circadian rhythms (Zaki et al., 2020). Research is growing on social factors that might influence sleep timing among retired individuals. Garefelt et al. (2021) suggested that schedules of household members and television viewing are likely to influence sleep timing. This current work identified that some individuals with T2D maintain an extremely consistent schedule of sleep and wake due to habit, retirement, age, ownership over the environment and daily constraints in the morning such as pets. However, we also identified some individuals with T2D who have fluctuating day-to-

day patterns and week to weekend patterns which occurred for three main reasons. The first reason was television viewing in the evening, and this ties in with what Garefelt et al. (2021) suggested. Participants often just let quality of TV determine sleep onset and, as a result, offset. This is a very simple behaviour that could be altered through education or sleep hygiene programs to promote better ownership over the environment before bed. This was intriguing because some of the individuals with consistent schedules actually commented on having a specific cut off point for watching TV every evening. It is important that these sleep hygiene recommendations are also taken seriously by participants as research has shown that knowledge of the importance alone is not sufficient to implement change (Brown et al., 2002).

Another factor leading to fluctuating sleeping patterns was household schedules which are difficult to change. Participants at times mapped their sleeping and waking behaviour onto their working family members. Providing education to the participants and the family members regarding the value of consistent, natural schedules could be beneficial where rise time is a choice. However, if the participants are waking to bring a family member to school or work then this is not an option. The idea of wanting to maintain some normality and enjoy oneself at the weekend also arose in many of the interviews. After retirement, many individuals do object to the idea of every day being the same. This points to a need to evaluate how important keeping this sense of 'normality' is to participants. Imposing consistent schedules may have a negative impact on psychological well-being for a few participants. Whether this sense of normality can be achieved through activities that do not influence sleep timing at the weekend needs to be considered. If so, simple behavioural interventions could be designed.

A diagnosis of diabetes yields a lifelong burden for many individuals, and this is something that needs to be considered when developing and suggesting treatment options. Participants with T2D are keen to learn about the disease but diabetes requires daily monitoring and additional stress to participants should be avoided. Some individuals experienced rumination, nocturia and age-related changes in sleep that acted to disrupt the ability to fall asleep and remain asleep and very clearly, could impact their sleeping patterns. Additional psychological support may be required for some participants to adjust to the 'shock' of a diagnosis and to help manage the new daily challenges that a diagnosis yields. Furthermore, T2D is a chronic disease with

significant burden associated with it, and when glycemic control is poor, people can find it challenging to manage. In order to control symptoms and reduce complications the work and care required by the affected person is unremitting (Corbin & Strauss, 1988; Ribu et al., 2019)

Taken together, this all suggests how it might be possible to target fluctuating sleep timing in modern society, especially in individuals without a regular work schedule. We also know that for a healthy lifestyle that diet, exercise, and sleep are crucial. Many biological activities are affected by sleep (Zaki et al., 2020). Growing evidence, which research from this PhD supports, suggests that minor circadian disruption can not only disrupt sleep but also influence body physiology (Zaki et al., 2020). Sleep and sleep timing are important for metabolic control; however, lifestyle recommendations for managing diabetes rarely go beyond diet and exercise. All of our interviewees reported that their diabetes team or consultant had never asked them about their sleep habits, and some participants had assumed that their sleep and diabetes management were completely unrelated. A few who took an active role in learning about the disease described being unaware of the importance of sleep until they carried out their own research. Very simple behavioural interventions might have the ability to improve disease management. However, many disciplines still do not consider the importance of sleep and chronobiology. Disciplines need to continue to integrate an understanding of the biological clock into treatment regimens. Building on our knowledge of chronobiology might reduce incidence and improve treatment outcomes (Zaki et al., 2020).

Another important finding from this current work is that common measures of the behavioural manifestations of circadian misalignment may not be related in the manner we assumed. In chapter 3 we identified an association between SJL and sleep end variability but not midsleep variability, sleep onset variability and sleep duration variability. Midsleep variability has been used as an indicator of circadian misalignment in some recent studies (Brouwer et al., 2020). Measures of circadian rhythm stability (IS) and variability (IV) also did not always correlate as expected. It is important to note that there may be scope for examining different measures of circadian misalignment in a single study in the future. This study allowed for good phenotyping of the sample but was restricted by power, so there is a need to evaluate whether this relationship consistently occurs in the population. Notably, the

participants in chapter 6 often described small variations in sleep and wake day to day but when asked for average sleep onset and offset time on week and weekend days, no SJL arose. This is because variations were not dependent on the day of the week but more so by the weather or how they were feeling on a given day. This suggests that for older adults not in employment, qualitative research which gathers in depth detail from the participants may be required. Alternatively, measures of sleep timing variability may also offer a truer picture of the variations in sleep timing among this population.

7.3 Reflecting on the Major Strengths and Limitations

One of the major strengths of this thesis is the diverse samples and datasets that we had access to. This was enhanced by the fact that the current work utilised both quantitative and qualitative research methods. This current work included cross-sectional research in a clinical sample (chapter 2) and non-clinical sample (chapter 4, study 1). It also entailed working with a small clinical dataset (chapter 3), and a large dataset from the UK Biobank (chapter 5). There was also an experimental aspect where stress reactivity was measured (chapter 4, study 2). This all gathered some useful quantitative data on the area of circadian misalignment, glycemic control, and stress. Chapter 6 gathered some rich qualitative data to answer our research question, which added depth to the knowledge gained.

For chapter 2, we had access to a clinical sample of participants with T2D. Outpatients were recruited directly from the diabetes annual review clinic at Connolly Hospital, Blanchardstown, Dublin. These patients tended to have uncomplicated diabetes, and this was a massive strength to the study. All participants were recruited from this slot and doctors and nurses helped obtain all the clinical measures needed. Patients tended to be very enthusiastic about participating and the majority were excited to share their opinions about their diabetes and their sleep. One thing noted here was how several participants had opinions and insights beyond the survey questions that they wanted to share. This was very helpful when designing the final qualitative study for people with T2D. Chapter 3 included a well detailed sample of controls and individuals with T2D and allowed comparisons between various measures of sleep timing. One of the most noteworthy things about this study is the level of detail it obtained on the participants and the variety of the measures of

circadian misalignment we had. Chapter 5 had one major strength which was the power that comes with big datasets. We had over 70 thousand observations on our desired measures of sleep timing. This enabled us to visualise these variables and investigate potential associations identified by previous literature but needed to be approached very carefully with an analysis plan prior to obtaining the data. Chapter 6 comprised rich data on participants' daily patterns by using reflexive thematic analysis to generate themes. This led to some important considerations for assessing sleep timing among an older cohort and for reducing day to day fluctuations in sleeping patterns.

Despite these strengths, a number of limitations existed that may limit generalisability of findings. A limitation to recruiting in the clinic was that everything moved at an incredibly fast pace. Up to 60 patients came in every Thursday morning between 8:30am and 12:30pm and since there was only one researcher, it was not always possible to invite everyone to participate. While many patients were content to participate, there was also a proportion of patients that were not interested and very rarely some became frustrated with the surveys and withdrew before completion. It needs to be considered that self-selection bias may have occurred. The participants may have been more proactive and interested in managing the disease. This could then influence the results collected. However, this is a limitation with most research that depends on voluntary participation. Another limitation was that we only obtained measures from a single time point so we could not observe any influence the variables of interest had over time on metabolic health. The association here also relied on self-report. More objective measures of sleep timing and diet would also have been useful in this instance.

Chapter 3 was restricted by the small sample. This meant that it was underpowered and only allowed for exploratory analysis. Much more research is needed on these measures of sleep timing variability before definitive associations can be determined. Research on what could be deemed normal variability is required to determine if these participants were showing sufficient variability for it to have a negative impact on health. While the UK Biobank had many observations, less detailed responses were obtained which was a limiting factor in terms of what conclusions could be drawn about human behaviour. Firstly, longer objective measurement where there were at least two week and weekend cycles would be useful

in order to provide a more accurate picture of weekday to weekend day sleep offset differences. Also, this resource involved measurements at different timepoints. It is crucial to remember that there may have been changes in some of the cardiometabolic variables between the initial recruitment and the collection of accelerometer data.

Chapter 4 demonstrated that in the general population there was no association between stress and SJL, allowing us to suggest that stress does not explain the association between SJL and glycemic control in chapter 2. However, this conclusion would have been stronger if work-stress had been assessed as a part of chapter 2. It is important to emphasise that this was not the aim of the research at the time and its suggested role came from our findings in younger participants. Further, as discussed above, some participants might have been frustrated with additional questionnaires, so it was important to keep this to the core measures to reduce participant burden. Some of our participants in chapter 4 were students. Calculating SJL in students can be difficult because their weekday schedule is not necessarily the same day to day with lectures, and sometimes students also work part-time at the weekend. To limit this effect, participants were asked to take a college day with lectures as a workday and excluded if they had no 'free days'.

One unavoidable limitation that occurred during the current work was the COVID-19 pandemic and the studies as part of chapter 4 and 6 were impacted as a result. As noted in the discussion for chapter 4, recruitment for study 1 had to be paused for 6 months in 2020 while Ireland first dealt with the COVID-19 pandemic. When things started to improve, further participants were recruited but the unavoidable change in working patterns that was beyond our control has to be acknowledged. However, it was assumed that participants would be acclimatising to living with COVID-19 at the time that we recommenced recruitment. Study 2 in chapter 4 was also impacted by the COVID-19 pandemic. Recruitment for this study was stopped prematurely in March 2020 as it involves close contact (less than 2 meters) between the researcher and the participant. This study involved measuring stress reactivity and given the changing nature of the pandemic, there were too many extraneous variables that might have compromised the experiment if continued. For example, participants might be uneasy with being in close contact with the researcher and this could then have an impact on their physiological markers of stress. Alternatively, participants would be wearing a mask, and this may increase anonymity

and reduce the socio-evaluative stress component where they are being watched and video-taped during the experiment. This study was reframed as a pilot study for future research.

The final study was also implicated by the pandemic as we could not directly access a sample of participants from the hospital due to the coronavirus. As a result, all participants were recruited online and through word of mouth. The findings may not be generalisable to the wider population of people in Ireland with T2D, as the group that volunteered could be more conscious of their diabetes disease management. However, we did get a very diverse description of experiences with T2D in the interviews. As interviews could not be conducted face-to-face, body cues could not be observed. However, as described in chapter 6, this has benefits as well as limitations.

7.4 Future Directions

There are some gaps in the literature that future research needs to evaluate. Developments in modern society have increased the efficiency of economic activity, and this is likely to continue to increase in the coming years. There is now 24/7 access to artificial light, and the internet, which means that many factories and businesses can operate on a 24/7 basis (Shepard Jr et al., 2005). This development promotes an environment where individuals can travel, socialise, and work during the body's biological night when the endogenous circadian clock is promoting sleep. These changes are accompanied by circadian misalignment. Research is growing to suggest that SJL increases risk of later life disease and is associated with poorer management of metabolic health and T2D. Some of the current findings also suggest that weekly circadian misalignment may have a negative effect on glycemic control among Irish patients with T2D. However, why this occurs in some studies and not others is unknown. For example, week to weekend day sleep offset differences was not associated with HbA1c in the UK Biobank. This is, however, very reflective of the current field of research and following on from this thesis, we need to start identifying what the differentiating factors are.

In future we need further studies with different populations, from different cultures investigating all of these parameters, namely circadian misalignment, and indicators of T2D disease control, in detail. Chronotype and SJL vary depending on the culture. For example, Reutrakul et al. (2013) conducted a study in the US and the

average MSFsc was 3:29 am with median SJL of zero minutes. This chronotype is slightly earlier than the one reported in chapter 2 and the SJL is also lower (MSFsc mean = 3:53 am, SJL median = 0:15 minutes). The difference between our sample and those from Rush is not that large (around 25 minutes for chronotype and 15 for SJL) but may explain in part why we identified an association between SJL and glycemic control and their study did not. This later MSFsc may have made our sample more vulnerable to SJL and this then could have had an impact on glycemic control. The US, Ireland and many European countries are very similar in respect of these measures of circadian rhythms. However, if we look at another study discussed in this thesis by Anothaisintawee et al. (2017) it can be observed that MSFsc is much earlier in Thailand (*M* = 1:57am), and median SJL was also zero minutes. Mota et al. (2021) recently reported median MSFsc as 2:50 am in Brazil, which is also lower than our average. They also reported 25% of participants had SJL greater than 1 hour. These cultures with varying circadian phase estimates and circadian misalignment estimates make it very hard to develop universal treatments and this is something to consider in future. Furthermore, this may be relevant to research beyond metabolic health, as SJL has been implicated in other health domains including mood and depressive symptoms (Levandovski et al., 2013). The development of a national diabetes registrar for adults in Ireland would be beneficial because estimating prevalence is limited by this factor (Treacy et al., 2016). This would also help identify the specific need for interventions.

Measures of cardiometabolic health also vary between cultures. For example, if we look at BMI in the study by Reutrakul et al. (2013) mean BMI among people with T2D tends to be higher in the US than our sample (M = 35.6 vs M = 32.1) and this will also impact metabolic health and glycemic control. While these variables are often controlled for in analysis, it is still important that these are acknowledged. The exact health risk that may occur with circadian misalignment and the variations in this between cultures needs to be discovered. Notably, a slight increase in health risk is enough to impact public health (Caliandro et al., 2021).

Furthermore, the mechanism by which SJL results in morbidity is unknown. Most of what we know about SJL, and other behavioural indicators of circadian misalignment, and how they impact health, come from epidemiological, cross-sectional studies (Caliandro et al., 2021). This has been extremely useful in determining associations. However, these studies involve a level of heterogeneity

which can often be a problem when researching people outside the laboratory and in the real world. Factors including duration of SJL and the amount of SJL can vary substantially between people, and this prevents us from drawing causal relationships. Studies which can ascertain causation are likely to be costly and time consuming but worthwhile to determine the true relationship between SJL and health.

Information on the long-term effects of circadian misalignment are also needed. Mota and colleagues (2021) recently conducted a retrospective, longitudinal study and identified that over a year, SJL was linked to changes in fasting glucose in the full sample with NCDs and those specifically with T2D. Further research to confirm this in cultures outside of Brazil are needed. In addition to this, longer-term studies are required with good characterisation of chronotype, SJL and metabolic health. Prospective longitudinal designs might be beneficial here. It is salient that we learn from chapter 3 and 5; we need a sample large enough and with good detail to be meaningful.

Beyond the use of longitudinal designs, future research in sleep science and chronobiology needs to consider the utility of qualitative research in addition to quantitative research. The value of quantitative research is well understood in the field as it can provide population level information on the causes, and risk factors, of various diseases, as well as information on prevention and treatment strategies (Jack, 2006). However, this does not always translate easily into healthcare and often more in-depth information might be required to make decisions by healthcare practitioners (Jack, 2006). Qualitative research can be reflexive (Braun & Clarke, 2019) and can provide rich detail on how people act and manage day-to-day settings. Essentially, most public health issues, including T2D are complex in nature and quantitative data may not always provide the depth of understanding that decision makers need (Jack, 2006). It is paramount to listen to individuals' personal perspectives as this can guide clinical practice (Jack, 2010). This may explain why the research on sleep and chronobiology has not been taken as seriously as it should be by many medical specialities. Qualitative research may help bridge that gap by providing additional insights and answer 'why' people engage in certain behaviours (Jack, 2006).

In the field of sleep science and chronobiology and more specifically the relationship between circadian misalignment and T2D, there is much more

information to be discovered in many different cultures and qualitative research has the ability to enrich understanding. Also, qualitative research is no longer viewed as just a precursor for quantitative research; qualitative research, if done well, can be used to inform policy and clinicians (Jack, 2006). Using qualitative and quantitative research needs to be balanced and this is clear from this thesis. Some very interesting findings were observed in chapters 2-5; however, the rich information around what influences sleeping patterns and daily routines in people with T2D would not have been obtained through quantitative research alone and can be used to guide interventions or very simple recommendations. Furthermore, how effective intervention strategies are is also limited and qualitative research of participants experiences will be crucial in evaluating the success of any interventions.

Society is likely to continue advancing in the coming years, so we need to learn how best to adapt an individual's circadian rhythms to the demands of modern society. Methods to prevent mistimed sleep and insufficient sleep are needed (Shepard Jr et al., 2005). Individual strategies to reduce SJL could be recommended; for example, reducing blue light exposure before bed (i.e., turning of electronic devices an hour before bed, or removing screens from the bedroom) and increasing blue light in the morning (i.e., through spending more time outdoors; Caliandro et al. 2021). The National Sleep Foundation recommends turning off all electronic devices the hour before bed in order to reduce the effect this light may have on sleep onset. Other interventions to alter the lighting environment and reduce circadian misalignment, including the use of blue light blocking glasses in the evening or opening curtains in the morning to let in more light have also been tested. Zerbini et al. (2020) noted no reduction in SJL with either condition but did note earlier sleep onset and an advance in melatonin on workdays after one week of blue-light blocking glasses. This was not significant at week two, reinforcing how changing the light environment is a difficult task. Better sleep hygiene could be adopted by all members of society, and this has been shown to have a significant impact on sleep quality (Brown et al., 2002). Whether this can also reduce circadian misalignment remains to be evaluated. More research into how we can adapt is necessary and this can then be used to inform policy and try to reduce the negative impact that modern society is having. Social strategies could also be considered which might allow more flexible work start times, as this may then reduce the amount of SJL experienced by workers (Caliandro et al., 2021).

One avenue of research here could be to determine what a normal level of variability is and then keeping the variability as low as possible but below this threshold. Even people with very consistent schedules do not fall asleep and wake up at the exact same moment every day. There may be a certain level of variability or SJL that does not exert the same negative effects. Some studies for example seem to take less than or greater than an hour as an indicator of SJL (Mota et al., 2017; Mota et al., 2021). A study by Monk et al. (2011) suggested that variability greater than 15 minutes in elderly people was associated with poorer sleep quality. It may be that greater amounts of misalignment have the worst effects. We know that large deviations as seen with shift work can be problematic for health and a study by Taylor et al. (2016) demonstrated that in their sample, that moderate variability had a negative impact on metabolic health. This might also explain some of our findings from chapter 3. It is possible that the variability in our sample was not large enough to exert the expected effect on our indicators of metabolic health. What constitutes a normal amount of variability has not been established but it is definitely a worthwhile avenue for research (Gooley, 2016).

7.5 Concluding Remarks

This thesis was conducted to evaluate the role of circadian misalignment in T2D disease management. This thesis also aimed to determine what factors influence this misalignment that might in turn impact metabolic health in those in the general population and with a diagnosis on T2D. We demonstrated that chronic circadian misalignment rather than later chronotype, personality factors or stress may play a role in glycemic control in T2D. Furthermore, we noted the need to evaluate different behavioural manifestations of circadian misalignment and to determine what a normal or minimally disruptive amount of each might be for optimal metabolic health. We also demonstrated that older adults, not in employment, can display weekday to weekend sleep offset differences and SJL. Reducing this in all age groups may have beneficial effects on metabolic health, especially in those with impaired glycemic profiles. This was an interesting finding because it is very well established in the literature that people display SJL and weekday to weekend day sleep timing differences when working. However, this is a very hard concept to intervene with (Zerbini et al., 2020). Importantly, with a greater understanding of what causes this misalignment in a non-working T2D sample, behavioural and sleep targeted

interventions could be developed. Our findings suggested that some of the factors influencing sleep timing and causing fluctuating sleeping patterns were quality of TV programs, the desire to maintain a sense of normality and derived zeitgebers from family members. Night-time disruptions were also very prevalent. In addition to this, we gained invaluable information on what guides consistent schedules in a subgroup of participants. Notably, medication or insulin-use did not tend to influence sleep or wake times. These findings might be helpful in guiding future strategies to reduce circadian misalignment and improve T2D management.

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Appendices

Appendix A

Glossary of Important Metabolic Terms.

Term	Brief definition
Adipocytes	Fat cells
Adipogenesis	The differentiation of preadipocytes into adipocytes. Essentially the formation of adipocytes.
Dysglycemia	Abnormality in blood sugar stability.
Dyslipidemia	Abnormality in level of cholesterol and other lipids in the blood.
Gluconeogenesis	Glucose formation: The process where glucose is formed when glycogen stores are depleted. *Glucose is formed from precursors including glycerol and glucogenic amino acids (non carbohydrate). In diabetes where the individual may not respond appropriately to insulin or may have inadequate production of insulin hyperglycemia can be worsened in individuals because gluconeogenesis occurs at an unusually rapid rate. Metformin acts in a variety of ways to suppress hepatic gluconeogenesis and help manage T2D (Melkonian et al., 2020).*
Glucose homeostasis	Normal blood glucose levels maintained by a balance between insulin and glycogen.
Glycolysis	Breaking down of a glucose molecule into two molecules of pyruvate (in the presence of oxygen) or two molecules of lactate (in the absence of oxygen).
Glycogenesis	Glycogen synthesis: glycogen is formed from glucose as glucose molecules are added to glycogen for storage. This is stored until needed at a later time.
Glycogenolysis	The biochemical pathway where glycogen is converted to glucose. This occurs when energy is needed by the body as the preferred energy source is glucose.

	Glycogen is the main form that glucose is stored in, and this is an important process involved in maintaining normal blood glucose levels during the fasting period and the liver plays a central role here (Paredes-Flores & Mohiuddin, 2020).
Hepatocytes	Liver cells, or more specifically parenchymal cells in the liver. They are important for metabolism.
Hormone	Chemical messenger in the body
Orexigenic hormone	Stimulates appetite and may cause hyperphagia e.g., ghrelin.
Anorexigenic hormone	Suppresses appetite e.g., insulin and leptin
Hyperglycemia	High levels of glucose in the blood due to inadequate production or response to insulin.
Hyperleptinemia	Hyper secretion of leptin, resulting in excess leptin levels in the blood. This is often implicated in diet induced obesity (Unger, 2005).
Hyperlipidemia	Elevated lipid levels in the blood. More specifically low-density lipoprotein (LDL), total cholesterol, triglyceride levels or lipoprotein levels above the 90th percentile when compared to the general population or high-density lipoprotein (HDL) below the 10th percentile when compared to the general population (Fredrickson, 1971).
Hypoglycemia	Low levels of blood glucose in the blood.
Insulin resistance	Diminished tissue response to insulin
Insulin deficiency	Insufficient insulin secretion
Post-prandial glucose	Plasma glucose concentrations after food intake
Rate limiting enzymes	The activity of this enzyme determines the rate of a given metabolic pathway.

Appendix B

The Munich Chronotype Questionnaire (MCTQ; Roenneberg et al., 2015)

Munich ChronoType Questionnaire (MCTQ)

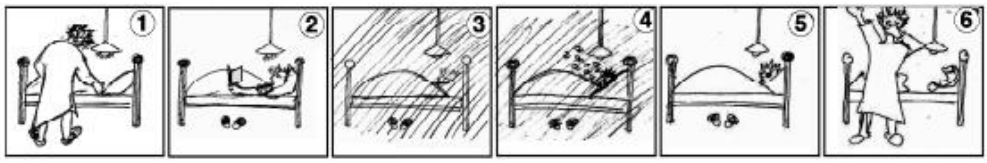
In this questionnaire, you report on your typical sleep behaviour over the past 4 weeks. We ask about work days and work-free days separately. Please respond to the questions according to your perception of a standard week that includes your usual work days and work-free days.

I have a regular work schedule (this includes being, for example, a housewife or househusband):

Yes ☐ I work on 1☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐ days per week.

No ☐

Is your answer "*Yes, on 7 days*" or "*No*", please consider if your sleep times may nonetheless differ between regular 'workdays' and 'weekend days' and fill out the MCTQ in this respect.



Please use 24-hour time scale (e.g. 23:00 instead of 11:00 pm)!

Workdays

Image 1: I go to bed at _____ o'clock.

Image 2: Note that some people stay awake for some time when in bed!

Image 3: I actually get ready to fall asleep at _____ o'clock.

Image 4: I need _____ minutes to fall asleep.

Image 5: I wake up at _____ o'clock.

Image 6: After _____ minutes I get up.

I use an alarm clock on workdays: Yes ☐ No ☐

If "Yes": I regularly wake up BEFORE the alarm rings: Yes ☐ No ☐

Free Days

Image 1: I go to bed at _____ o'clock.

Image 2: Note that some people stay awake for some time when in bed!

Image 3: I actually get ready to fall asleep at _____ o'clock.

Image 4: I need _____ minutes to fall asleep.

Image 5: I wake up at _____ o'clock.

Image 6: After _____ minutes I get up.

My wake-up time (Image 5) is due to the use of an alarm clock: Yes ☐ No ☐

There are particular reasons why I cannot freely choose my sleep times on free days:

Yes ☐ If "Yes": Child(ren)/pet(s) ☐ Hobbies ☐ Others ☐, for example:_____

No ☐

Appendix C

The Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989)

PITTSBURGH SLEEP QUALITY INDEX (PSQI)

INSTRUCTIONS: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, when have you usually gone to bed at night?

   USUAL BED TIME _____

2. During the past month, how long (in minutes) has it usually take you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, when have you usually gotten up in the morning?

   USUAL GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.)

   HOURS OF SLEEP PER NIGHT _____

INSTRUCTIONS: For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a) ...cannot get to sleep within 30 minutes	☐	☐	☐	☐
(b) ...wake up in the middle of the night or early morning	☐	☐	☐	☐
(c) ...have to get up to use the bathroom	☐	☐	☐	☐
(d ...cannot breathe comfortably	☐	☐	☐	☐
(e) ...cough or snore loudly	☐	☐	☐	☐
(f) ...feel too cold	☐	☐	☐	☐
(g) ...feel too hot	☐	☐	☐	☐
(h) ...had bad dreams	☐	☐	☐	☐
(i) ...have pain	☐	☐	☐	☐
(j) Other reason(s), please describe _____ _____				
How often during the past month have you had trouble sleeping because of this?	☐	☐	☐	☐

PSQI Page 1

	Very good	Fairly good	Fairly bad	very bad
6. During the past month, how would you rate your sleep quality overall?	☐	☐	☐	☐

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
7. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?	☐	☐	☐	☐
8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	☐	☐	☐	☐

	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?	☐	☐	☐	☐

	No bed partner or roommate	Partner/ roommate in other room	Partner in same room, but not same bed	Partner in same bed
10. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?	☐	☐	☐	☐

If you have a roommate or bed partner, ask him/her how often in the past month you have had...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a) ...loud snoring	☐	☐	☐	☐
(b) ...long pauses between breaths while asleep	☐	☐	☐	☐
(c) ...legs twitching or jerking while you sleep	☐	☐	☐	☐
(d) ...episodes of disorientation or confusion during sleep	☐	☐	☐	☐
(e) Other restlessness while you sleep; please describe	☐	☐	☐	☐

_____

_____

Appendix D

Protocol for Chapter 4 (Study 2).

Study B. Stress Reactivity and Social Jetlag Protocol Overview

Participant ID number:_____ Date & Time: _____

Code all questionnaires being used.

Participant Arrival

"Hello, your name is (XXXX), is that right? My name is _____.Welcome and thanks for coming in to us today."

> "You can leave your things here (refer to empty table by door). Please have a seat over here. I'll just give you the Information Sheet to read through. Please let me know when you're finished."

→ *Wait until participant has read information sheet*

Do you have any questions?"

→ *Address questions if necessary*

"Please read this sheet as well, and if you're okay with everything, then please sign it at the end."

→ *Provide consent form & collect once signed*

"I will talk you through the blood pressure measurements, and the tasks shortly. Before we begin, I need to check a few things. Have you….."

Checklist

Consumed alcohol in the last 12 hours?	☐ Yes	☐ No
Participated in vigorous exercise in the last 3 hours?	☐ Yes	☐ No
Smoked in the last 3 hours?	☐ Yes	☐ No
Consumed caffeine in the last hour?	☐ Yes	☐ No
Eaten in the last hour?	☐ Yes	☐ No
Also, are you right-handed or left-handed?	☐ Right	☐ Left

"What age are you?"

"And what is your gender?"

"Great, now, can I ask you to step here so that I can measure your height and weight?"

Height (cm):_____ Weight (kg):_____

"Thank you! You can take a seat again."

"Today, we are going to take some blood pressure measurements from you while you complete a task in the lab."

"Please place your feet on the box and keep them there throughout the study. This is to control for movement which might affect the blood pressure readings. During the session please do not speak unless you're asked to, as this could alter the blood pressure readings. I will explain what is expected as we go along and I can answer any questions you have at the end. Is that OK?"

"This blood pressure cuff applies pressure to the arteries in the arm for the purpose of measuring blood pressure. I am going to wrap the cuff around your upper non-dominant arm at the level of the heart. At several times throughout the session the cuff will be inflated, so that we can get the blood pressure reading. After it inflates and we have a reading it will start to deflate immediately."

"The cuff can get a little tight, but the discomfort will subside. We will run a practice measurement so that you can see how it feels. Please keep your arm straight while measurements are being taken."

→ *Attach sleeve to non-dominant arm, tubes placed on the upper side of arm and run practice measurement.*

"Was that alright? If the cuff is quite uncomfortable, I can adjust if for you now."

→ *Adjust cuff if necessary*

"If you feel uncomfortable again please let me know. Otherwise, to make sure we have accurate measurements, it would be helpful if you could remain silent during the tasks."

End of acclimatisation: "I am going to get you to relax for a few minutes and you can look at this magazine if you wish. Following this you will be doing three minute stress reactivity task. We will take a few blood pressure measurements throughout." (Start of Baseline)

Resting Period

Take baseline BP measurements at 0 minutes. Then administer the KSS.

Stress Reactivity Task

"You will now be doing a stress task. The instructions are written here for you to read."

→ *Ask participant do you understand?*

A tank filled with water is placed next to the participant. The experimenter will stand in front of the participant, with some distance to the camera, so that participant, camera and experimenter form an equilateral triangle and the participant can see the experimenter from the corner of his/her eye while looking into the camera. The experimenter will be beside the blood pressure machine. If everything is set-up, the experimenter asks the participant to immerse his/her hand into the ice water.

→ *Take BP measurements upon hand submersion, and 1 minute after submersion.*. After 3 minutes the participant will be asked to remove their hand from the water and told that the task is now over. Immediately after participants take their hand out of the water, they will rate on an 11-point scale ranging (in 10-point increments) from 0 ("not at all") to 100 ("very much") how unpleasant, stressful and painful the previous situation had been.

-"I have a few questionnaires for you that I'd like you to complete. You will have approximately 15 minutes to do that, but if you take longer that's no problem. If you're done early, you can take a look at the magazine.

→ *Provide questionnaire booklet (MCTQ, PSQI)*

→ *Obtain BP reading after 15 minute resting period.*

→ *Take off blood pressure cuff*

Debriefing:

> "Thank you very much for participating!" "The stress-reactivity task was just to assess if different circadian rhythms were associated with higher or lower stress responses" Do you have any questions?"

→ *Address questions.*

"Thanks again for participating!"